Clinical Profile and Response to First-Line ARV in HIV Patients from Eastern UP and Bihar: A Retrospective Study

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Abstract

Background and objectives: Spectrum of infections in Human Immunodeficiency Virus (HIV) infected patient from Eastern UP and Bihar has not been systemically evaluated. This study was conducted with the following objectives; a) explore the spectrum of clinical conditions associated with HIV disease, b) the difference between clinical and investigatory parameters in those patients who presented with infection from those who present without infection and c) to evaluate the effect of anti-retroviral (ARV) therapy.

Methods: 1248 subjects who fulfilled the inclusion criteria were enrolled for the study from May 2007 to November 2008. Patients were evaluated for their baseline characteristics along with CD4 count and followed up for at least for 6 months after initiation of ARV (6-24 months).

Result and interpretation: In this retrospective study, tuberculosis (58.96%) was the commonest infection followed by chronic diarrhoea (26.56%) and various skin infections. Males had significantly higher incidence (p value<0.001) of infection as compared to females. There was a significant difference between the patients who presented with infection from those who presented without infection for their baseline weight (42.3 vs 45.42), haemoglobin (9.06 vs 9.91), mean CD4 count at baseline (107.38 vs 128.38/µl) and CD4 count after 6 month of therapy (298.09 vs 322.98 /µl). Mortality was also significantly high (p value<0.05) in those who presented with infection (19.95% vs 15.1%), although there was no difference between these two groups on their improvement in CD4 count from baseline after 6 months of therapy.

Conclusion: Among the spectrum of infection in HIV patient from North East part of India, tuberculosis was commonest, followed by skin infections and chronic diarrhoea. Patients who presented with infection at the time of initial presentation had a low haemoglobin, body weight and CD4 count and had high initial mortality but if they survived they show similar response to ARV therapy as patients who presented without infection.

Introduction

A fter the detection of first case of HIV disease,1 the HIV/ Acquired Immunodeficiency Syndrome (AIDS) epidemic is nearly 29 years old. During the initial years, the major focus was on prevention activities followed by care and support of infected individuals particularly those suffering from associated infection including Opportunistic Infections (OIs). Opportunistic infections have been recognized as common complication of HIV infection2,3 from the very beginning of HIV epidemic. It causes substantial morbidity and hospitalization, necessitates toxic and expensive therapy and shortens the survival of HIV infected patients.4-6 The spectrum of infections in HIV infected person varies in different countries; like the most common OIs in Italy is P. jirovecii,6 while cytomegalovirus (CMV) infection is most frequently seen in Mexico7 and tuberculosis in Africa.8 As the number of AIDS cases increase in India,9 little information is available about the prevalence of OIs, more so from Eastern UP and Bihar.

A decrease in CD4 counts is at least partially responsible for profound immunodeficiency that is responsible to various opportunistic infections in HIV infected person.10 Providing prevention and treatment of various infections not only help HIV positive person to live longer, but it can also help to prevent tuberculosis and other transmissible infections from spreading to others. Untreated HIV infection involves gradual depletion in the peripheral blood CD4 lymphocyte count from normal levels of around 900 cells/µl to as low as < 10 cells/µl, which results in risk of AIDS defining diseases and death.11,12 The rate of decline in CD4 count varies between individuals and is thought to be largely determined by the rate of HIV replication, as measured by the plasma HIV RNA level.13 Therapy with antiretroviral drugs induces substantial reductions in plasma HIV RNA levels, which reverses the downward trend in CD4 lymphocyte counts.14-18

Materials and Methods

We reviewed the data of 1248 HIV positive patients who attend the outpatient department of ART Centre of Department of Medicine, Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, from June 2007 to November 2008, or were admitted in Medical Ward. This centre works as a Centre of Excellence for the patient of HIV infection or AIDS in this part of country. The catchment area of this hospital includes the patients mainly who came from Eastern part of Uttar Pradesh and Bihar.

The study group consisted of patients with age more than

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15 years, confirmed diagnosis of HIV infection, who fulfilled the National AIDS Control Organization (NACO) criterion to be classified as AIDS and were ART naive. The patients fell in three groups: 1) CD4 level <200/µL irrespective of clinical staging, 2) CD4 in between 200 to 350/µL with WHO clinical stage III and 3) WHO clinical stage IV irrespective of CD4 count. The diagnosis of HIV infection was assessed by three different methods as ERS (ELISA, Rapid, Simple) as recommended by NACO, Ministry of Health and Family Welfare, Government of India.24 All tests were performed in the Department of Microbiology, Sir Sunderlal Hospital, Banaras Hindu University.

All the patients were investigated for CBC, serum creatinine, SGOT, SGPT, HBsAg, Anti-HCV, VDRL and Chest X-ray (PA view). CD4 count was done by FACS counter (Becton Dickinson).

Diagnosis of associated infection

For the diagnosis of various infections, detailed history and clinical examination (Including the Skin, Oropharangeal cavity, Genitalia along with Systemic examination) of each and every patient was done thoroughly. Genuine efforts were made to establish the diagnosis of an infection, microbiology of smears of relevant sample, cultures and serology were performed. However, sometimes, at the time of initial presentation patients were too sick to undergo invasive diagnostic procedures such as bronchoscopy or tissue biopsy and hence the following criteria were used to define an infection (including OIs) concerned. Pulmonary tuberculosis (PTB): clinical features suggestive of TB along with radiological features compatible with TB on chest radiograph or computed tomographic scan (CT) and/or demonstration of acid-fast bacilli (AFB) in sputum smears or growth of *Mycobacterium tuberculosis* in sputum culture; Abdominal tuberculosis: clinical features suggestive of TB along with Ultrasound(abdomen/pelvic), finding suggestive of abdominal tuberculosis and improvement with anti tubercular treatment. Disseminated tuberculosis (DTB): clinical features suggestive of TB with concurrent involvement of at least two or more non-contiguous organs, in the presence of bacteriological and/or histopathological evidence of TB and improvement with anti-tuberculosis therapy; miliary tuberculosis (MTB): clinical presentation consistent with TB and bacteriological and/or histopathological evidence of TB and demonstration of bilateral miliary infiltrates on chest radiograph or high-resolution CT; tuberculosis meningitis (TBM): clinical and cerebrospinal fluid (CSF) features consistent with tuberculosis meningitis, and/or bacteriologic demonstration of *M. tuberculosis* in CSF and after exclusion of other aetiologies such as cryptococcus and syphilis, with evidence of tuberculosis elsewhere and/or improvement with anti-tuberculosis therapy; cryptococcal meningitis: in CSF, demonstration of *Cryptococcus* sp. yeast cells by India ink or antigen by latex agglutination or growth in culture; cerebral toxoplasmosis: demonstration of multiple ring-enhancing cerebral parenchymal lesions on contrast-enhanced CT or magnetic resonance imaging (MRI), in the presence of anti-toxoplasma antibody in serum and clinical response to anti-toxoplasma therapy; progressive multifocal leuкоencephalopathy (PML): compatible clinical presentation with demonstration of characteristic cerebral white matter changes by MRI; *Pneumocystis jiroveci* pneumonia (PCP): bilateral, diffuse interstitial infiltrates on chest radiograph or high-resolution CT, with hypoxemia (PaO₂ <12 kPa or 90 mm of Hg) and sputum smears/cultures negative for aerobic bacteria and AFB and/or demonstration of *Pneumocystis jiroveci* in induced sputum and improvement with Co-trimoxazole therapy. For the diagnosis of skin disorder, compatible clinical presentation along with physical signs and demonstration of organism by staining in skin scraping or in diagnosed tissue and/or growth in culture. CMV retinitis: clinical feature suggestive of ocular involvement along with demonstration of specific lesion on fundus examination. No attempt was made to isolate organism from the stool of the chronic diarrhoea patient.

Anti-retroviral (ARV) Therapy

ARV therapy was started in all patients according to NACO guideline:20 two NRTI and one NNRTI regimen used as a first line ARV therapy. Two regimens were used.

i. Zidovudine + Lamivudine as an NRTI and Nevirapine (Efavirenz in patient on anti-tubercular treatment)

ii. Stavudine + lamivudine as an NRTI and Nevirapine (Efavirenz in patient on anti-tubercular treatment).

Haemoglobin value 8 gm/dl taken as cut off for anaemia to decide which regimen was started. Patient below Haemoglobin level 8 gm/dl put on stavudine-based regimen. All the patients were counselled about the natural course of disease and its different modes of transmission, importance of treatment adherence in spite of symptomatic improvement, life long therapy, importance of family screening, use of barrier contraception or abstinence in discordant couples and importance of regular follow up.

Follow-up

All patients were followed up at least for 6 month (6-24 month). Patients were examined on monthly basis for clinical improvement and sign of development for various infections, tolerability of drug and their side effect. Haemoglobin level was done on monthly basis in patients who were on zidovudine based therapy. Patients who develop anaemia were switched to stavudine based therapy during follow up. CD4 count was done every 6 monthly.

Statistical Analysis

Occurrence of infections with their corresponding CD4 count was recorded. Entered data was cross checked for discrepancies. Analysis of all data was done using SPSS for windows (version 16.0). Data was presented as mean ± SD. Frequency of various clinical and laboratory findings of individual infections were expressed as proportions. Paired ‘t’ test was applied to assess the improvement in CD4 counts following antiretroviral therapy. A ‘p’ value <0.05 was regarded as statistically significant.

Results

In this study, a total 1248 patients were studied. Mean age of patients was 36.23±8.70 (16-70). Of these, 892 patients (71.47%) presented with one and more than one infection as the time of initial presentation (group I). 972(77.88%) patients belong
Distribution of infection

Among the spectrum of infection observed, tuberculosis was the commonest infection, occurred in 526 patients (58.96%).

Table 1: Baseline characteristic of patients

<table>
<thead>
<tr>
<th>Patients with infection; group I</th>
<th>Patients without infection; Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>892 (71.47%)</td>
</tr>
<tr>
<td>Sex distribution</td>
<td></td>
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<tr>
<td>Male</td>
<td>672 (75.33%)</td>
</tr>
<tr>
<td>Female</td>
<td>220 (24.67%)</td>
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<tr>
<td>Ratio</td>
<td>3.05</td>
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<tr>
<td>Age (mean ± SD, range)</td>
<td>36.35±7.70 (16-70)</td>
</tr>
<tr>
<td>CD4 count (per µL)</td>
<td></td>
</tr>
<tr>
<td>At 0 month</td>
<td>107±60</td>
</tr>
<tr>
<td>At 6 month</td>
<td>298±148</td>
</tr>
<tr>
<td>Improvement in CD4 count (0-6 month)</td>
<td>162(83.0,263.5)</td>
</tr>
<tr>
<td>Baseline haemoglobin (gm/l)</td>
<td>9.06±2.15</td>
</tr>
<tr>
<td>Baseline weight (kg)</td>
<td>42.3±2.15</td>
</tr>
<tr>
<td>Mortality (during 6-24 month of follow up)</td>
<td>178 (19.95%)</td>
</tr>
<tr>
<td>No. of new infections during 6 month follow up (per 100 pts)</td>
<td>52 (6.2)</td>
</tr>
</tbody>
</table>

Fig. 2: Distribution of infection

Mean CD4 of pulmonary tuberculosis was 110.39/µL (6-419). CD4 of most of extra-pulmonary tuberculosis was less as compared to pulmonary tuberculosis (Table 2). As the data shows, tuberculosis occurred over wide range of CD4 counts (6-419/µL).

The second most common infection was chronic diarrhoea which occurred in 237 patient (26.56%) with mean CD4 of 100.81/µL (5-309/µL). No attempt was made to find out pathological organism. In the spectrum of infection observed, various skin infections were the next with the frequency of, scabies in 102 patients (11.43%), fungal infection of skin and nail in 85 patients (9.53%), herpes zoster in 48 patients (5.38%). Oral candidiasis was found in 107 patients (11.99%) with mean CD4 count of 81.69/µL (5-301) and four of these patient also have associated oesophageal candidiasis. The frequency of various infections along with their CD4 count is mentioned in Table 2 (Figure 2).

During follow up (6-24 month), 232 (18.6%) patient expired. 248 patients were transferred out to other centre for therapy and 156 patients (12.5%) lost to follow up (Figure 3).

Out of 1248 patients, 501 patients were put on zidovudine based regimen, 745 patients were put on stavudine based regimen and 2 patients, who were followed more than 6 month, showed treatment failure shift to 2nd line drug therapy. Mean CD4 count of 680 patients, from those who started on ARV therapy at the beginning, were available after 6 month of therapy. There was a significant improvement in CD4 (p<0.001) from before (122.78±70.06/µL) to after therapy (305.37±147.39/µL). Improvement in CD4 count of those patients who presented with infection (group I) and those who without infection (group II) and difference in other characteristics between these groups are mentioned in Table 1.

Discussion

HIV already has 33.4 million victims globally, and in India, it
figures around 3 million patients.\textsuperscript{2,2} An estimated 113 thousands HIV infected peoples live in UP (Panday et al.).\textsuperscript{2,23} The clinical spectrum of HIV infection in India is different from rest of the world. Within India also there is a lot of variability, as shown in different studies.\textsuperscript{2,4-29} The reason of this discrepancy might be the difference in the spectrum of various infections in different parts of our country. Infections are the major cause of morbidity and mortality in HIV patients. So, in a resource limited settings, knowledge regarding the prevention of various infections can help to cut down the cost burden of HIV disease.

We conduct this study on 1248 HIV patients to study the spectrum of various infection in the eastern UP and Bihar that was definitely a resource poor area along with to know the effect of ARV therapy.

Out of total cohort, 71.47\% patient presented with one and more than one infection. This high percentage is due to the fact that they presented to us when they became symptomatic. In some Indian studies this percentage goes up to 100.\textsuperscript{2,23} Patient who presented without infection were mostly those who were diagnosed early in the natural course of disease accidentally (during blood donation or routine investigation before surgery) or were spouses and children of infected person and diagnosed during screening. In the present study 20-40 age group patients was most commonly (77.6\%) involved. This is being the age of maximum sexual activity that also favours the sexual transmission as the dominant mode (68\%). These finding are consistent with other Indian studies.\textsuperscript{2,4-26} In most studies, male patients were predominant over female\textsuperscript{2,23} as in our study, male was 71.71\%. The reason for male predominance is the socio-economic structure of our country where male is the bread earners of the family. They go outside in metros and get infected.

As we discuss, sexual transmission is the most common mode of infection, heterosexual contact was the core, though we found 5 case of homosexual transmission, but that was very less in contrast to western population.\textsuperscript{30} The reason is that homosexual are culturally unacceptable in our country. Transmission by blood and blood product was only 2.1% that was a less from other Indian studies\textsuperscript{2,24} and that of NACO.\textsuperscript{31} A large proportion of patient (27.7\%), no definite history of exposure was available. The reason could be the social taboos associated with this disease.

Frequency of different infections (Table 2) in this study is almost similar to other Indian studies\textsuperscript{2,4,25,28} and data provided by NACO.\textsuperscript{31} Tuberculosis is being the most common. It was not surprising as the country like India, where it is highly prevalent even in non HIV patient. As expected, it affected patients over a wide range of CD4 count (6-419/\mu L); considering tuberculosis as AIDS defining illness, the patient with significantly higher CD4 count was also enrolled in the study. Similar to previous study,\textsuperscript{2,4} the organ found to be most commonly involved in extra-pulmonary tuberculosis in HIV infected patients were the GI system.

The current study, the prevalence of chronic diarrhoea was 26.53\% that was lower as compared to other Indian study.\textsuperscript{2,4} Excluding the skin disorder, oral candidiasis was found to be third commonest OI. Its prevalence was 11.98\% as compare to other Indian studies,\textsuperscript{2,24,25} where it ranged between 25 to 83\%. 5 patients with oesophageal candidiasis were also associated with this infection. Mean CD4 count of this infection was 81.69/\mu L(5-301) that was much lower as compared to other Indian study.\textsuperscript{2,4} We also report a lot of skin infection in current studies. They show a wide range of frequency as compared to other Indian studies.\textsuperscript{32,33} In the pre HAART era, CMV retinitis was one of important OI with prevalence of 30-40\%,\textsuperscript{35} but after the introduction of HAART therapy, there was a significant change in natural history of CMV retinitis.\textsuperscript{36} We diagnosed 5 cases of CMV retinitis in our study with a mean CD4 count of 50.20/\mu L(6-111).

We did not find out any case of Kaposi sarcoma, this finding is similar to the study done by MS Zabeer, et al.\textsuperscript{3} But, this is at variance with the NACO study\textsuperscript{31} that reported 8\% prevalence of Kaposi sarcoma in a study.

The lower mean CD4 of each infection seen in our study as compared to other Indian studies may be due to advanced stage of disease as the patient referred to tertiary care centre very late, so that the diagnosis remains uncertain or is not established until late stages.

In current study we compare the cohort of patients who presents with infection (group I) to those patients who present without infection (group II) at the time of initial presentation (Table 1). Number of male patients was significantly (p value<.01) high in infectious cohort that may be due to most of the female in non-infectious cohort were the wives of male patients in infectious cohort. There was a significant (p value<.001) difference between these two groups for their baseline weight (42.3 vs 45.42), haemoglobin (9.06 vs 9.91), mean CD4 count at baseline (107.38 vs 128.38) and CD4 count after 6 month of therapy (298.09 vs 322.98). Mortality was also significantly high (p value<0.05) in patients who presented with infection (group I).

But there was no significant difference between these two groups for their improvement in CD4 count after 6 months of therapy and the number of new infection during follow up/100 patients. This explain that patient who presented with infection at the time of initial presentation, although chance of their survival is less as compare to those who present without infection but when they survive, there was no difference in immunological recovery in between these two group on ARV therapy and show almost equal resistance to further new infection.

Conclusion

The result of current study clearly suggest that clinical profile of HIV infection in Eastern UP and Bihar is almost similar to rest of India with some differences. Tuberculosis is the most common infection followed by diarrhoea and various skin infections. Lower CD4 count of our study may be due to selection bias of these patients. Patients, who presented with infection at the time of initial presentation, had significantly low haemoglobin, low CD4 count and weight with high mortality but if they survive, showed equal rate of immunological reconstitution on ARV therapy as the patient who presented without infection. So, early pick up of patient from this infectious cohort by wide spread awareness of HIV infection, about its sign and symptoms and early referral of these patient to integrated counselling and testing centre (ICTC) will help to reduces the morbidity and mortality cost burden associated with this disease.

References


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