Nevirapine Versus Efavirenz Based Antiretroviral Treatment in Naïve Indian Patients: Comparison of Effectiveness in Clinical Cohort


Abstract

Objective: Our objective was to compare immunologic effectiveness of nevirapine and efavirenz based antiretroviral therapy in antiretroviral naïve HIV-1 infected Indian patients.

Design and Methods: Study was an observational, non-randomized, longitudinal cohort. Antiretroviral naïve HIV-1 infected patients receiving efavirenz + 2 NRTI (n=254) and nevirapine + 2 NRTI (n=857) from April 2000 were followed up at two tertiary care HIV clinics at Ahmedabad and Pune. Patients were followed up clinically monthly and CD4 was carried out every 3 monthly. All patients were examined for various side effects as well as development of various OIs. Data were analyzed using standard statistical methods.

Results: Baseline characteristics for both the groups (NVP and EFV) were comparable. In the random effects model, there was an increase of 40.97 (p < 0.05) units of CD4 cell counts with an unit increase in time in the NVP arm as against a 44.75 (p < 0.05) units of increase in CD4 cell counts in the EFV group with a unit increase in time, which is significant for both groups. However, at any given point of time there was no difference in the rate of increase of CD4 count between the two treatment arms (p=0.58). Hypersensitivity reaction (6.6% in NVP vs. 2.32% in EFV, p=0.0146) and hepatitis (3.2% in NVP vs. 0% in EFV, p=0.0085) were more common with nevirapine, while neurologic disturbances (0.93% in NVP vs. 20.15% in EFV, p=0.0001) were more common with efavirenz. Incidence of distal sensory neuropathy and lipid abnormalities was similar in both the groups.

Conclusion: Use of NVP and EFV based HAART in antiretroviral naïve Indian patients led to significant and durable rise in CD4 cell count. Although observational and non-randomized, our study showed equivalent immunological response amongst NVP and EFV based HAART which is in line with the results of the 2NN study.
follow-up period (never >12 months), and sometimes gave contradictory results as to potency and safety.23,24 In 2NN study virologic and immunologic efficacy was comparable when EFV and nevirapine were used in ART naïve subjects.25 In treatment-experienced patients, available uncontrolled data suggest these agents contribute to regimen efficacy in NNRTI-naïve, treatment-experienced patients. NVP and EFV have also been studied successfully as a replacement for a PI in a virologically successful regimen, with the aim of preventing or reducing PI toxicities and simplifying the dosing regimen.26-28 EFV based HAART is still expensive in developing countries like India. Nevirapine is widely preferred over efavirenz by patients and treating consultants due to low cost and availability as fixed dose combinations in our settings. In our study we tried to compare efficacy of both these drugs in antiretroviral naïve Indian patients.

**MATERIALS AND METHODS**

HIV 1 infected antiretroviral treatment naïve patient initiating nevirapine and efavirenz based HAART were recruited consecutively and followed up at Infectious Diseases Clinic, Ahmedabad and Ruby Hall clinic, Pune. Baseline demographic and clinical data were collected. All the patients were appropriately evaluated and treated for various opportunistic infections. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis was given in subjects with CD4 cell count < 200/cmm. Immunologic assessment was performed by peripheral CD4 lymphocyte count carried out by flow cytometry assay using FACS count. Plasma viral load assay was not carried out due to financial constrain.

**Treatment**: Generic antiretroviral drugs made by Indian pharmaceutical company were used. Patients in nevirapine arm were started with nevirapine 200mg/day for 14 days followed by 200mg twice a day along with two nucleosides. Patients in efavirenz arm were initiated with 600mg of efavirenz at bedtime along with two nucleosides. Nucleosides offered were either stavudine and lamivudine or zidovudine and lamivudine as selected by treating physician. Antiretroviral agents selected considering patient’s willingness, affordability, potential drug interactions or any contraindications to the use of particular drug.

**Clinical and laboratory evaluation**: All patients were followed up clinically every monthly or more frequently till clinical & immunological stabilization, then every 3 months. Patients were inquired in detail regarding symptoms suggesting development of opportunistic infections and various adverse effects related to drugs. Adverse effect (AE) was defined as any event judged by the investigator to be definitely, probably or possibly related to the administered drug (NVP/EFV). Adverse effects were graded and managed according to standard guidelines. Liver function tests were carried out as and when clinically indicated. Hepatitis was defined as asymptomatic elevation of ALT by 5 times or symptomatic elevation of ALT by 3 times the upper limit of normal. The evaluation of efficacy was carried out quarterly assessment of immunologic status by CD4 lymphocyte count. Adherence was assessed by self-report and counter questionnaires.

**Statistical analysis**: A two-sample t-test was performed to test for equality of age in each treatment groups. Mann-Whitney test was performed to test for equality of median age instead of mean age. To measure the rate of increase, we performed a longitudinal analysis. We fit a random effects model and then we look at multiple linear regression model for longitudinal data by specifying the within subject correlation.

**RESULTS**

**Subject**: Out of 1111 patients studied, 857 had received nevirapine and 254 had received efavirenz based HAART. Baseline characteristics of both the groups are shown in Table 1.

Mean age in the two treatment groups differ. The reason for this difference could be because of the wide range in the ages in both groups. In NVP group 214 patients were given AZT+3TC, while 643 were given d4T+3TC and in EFV group 36 patients were given AZT+3TC, while 218 were given d4T+3TC as 2NRTI. Gender distribution in both the group was comparable.

**Immunological response**: The baseline CD4 count was comparable in both the groups (p=0.17). In NVP group median CD4 count at baseline was 111 (2-741, n=857) cells/cmm. Thereafter-median CD4 counts at 3, 6, 9, 12, 15, 18 and 24 months were 260 (32-916, n=622), 291 (22-1108, n=673), 328 (63-936, n=329), 359 (25-1592, n=463), 382 (84-934, n=161), 382 (11-1833, n=235) and 425 (3-1564, n=97) respectively. In EFV group median CD4 count at baseline was 99 (2-613, n=254) cells/cmm. Thereafter-median CD4 counts at 3, 6, 9, 12, 15, 18 and 24 months were 238 (26-1751, n=238), 261 (23-1322, n=235), 292 (22-1108, n=673), 328 (63-936, n=329), 359 (25-1592, n=463), 382 (84-934, n=161), 382 (11-1833, n=235) and 425 (3-1564, n=97) respectively. In NVP group median CD4 count at baseline was 99 (2-613, n=254) cells/cmm. Thereafter-median CD4 counts at 3, 6, 9, 12, 15, 18 and 24 months were 260 (32-916, n=622), 291 (22-1108, n=673), 328 (63-936, n=329), 359 (25-1592, n=463), 382 (84-934, n=161), 382 (11-1833, n=235) and 425 (3-1564, n=97) respectively. In EFV group median CD4 count at baseline was 99 (2-613, n=254) cells/cmm. Thereafter-median CD4 counts at 3, 6, 9, 12, 15, 18 and 24 months were 238 (26-1751, n=238), 261 (23-1322, n=235), 292 (22-991, n=161), 338 (30-885, n=121), 398 (142-854, n=65), 382 (122-1163, n=47) and 377 (265-545, n=9) respectively. Comparison of serial CD4 cell counts is shown in the Fig. 1.

In the random effects model, there was an increase of 40.97 (p < 0.05) units of CD4 cell counts with a unit increase in time in the NVP arm as against 44.75 (p < 0.0004) in the EFV arm.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NVP (n=857)</th>
<th>EFV (n=254)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD) in years</td>
<td>36.14 (± 9.07)</td>
<td>37.65 (± 10.12)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>668 (77.9%)</td>
<td>188 (74.0%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Female</td>
<td>189 (22.1%)</td>
<td>66 (26.0%)</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 cell count (median)</td>
<td>111/cmm</td>
<td>99/cmm</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Table 1: Baseline characteristics
0.05) units of increase in CD4 cell counts in the EFV group with a unit increase in time, which is significant for both groups. However, at any given point of time there was no difference in the rate of increase of CD4 count between the two treatment arms (p=0.58).

Adverse events: Major adverse reactions reported in both the groups are shown in the Table 2.

From Table 2 it is evident that hepatitis and skin rashes were more commonly observed with NVP and CNS disturbances were more commonly observed with EFV. Incidence of lipid abnormalities and distal sensory neuropathy was similar in both the groups.

Discussion

Efavirenz based HAART is current standard of care in management of HIV infected patients with long-term efficacy data are available. In developing countries like India nevirapine based HAART is cheap compared to efavirenz based HAART. Efficacy and safety of nevirapine based HAART has been demonstrated in various studies in ART naïve patients.26

In our study both NVP and EFV arms had similar rise in CD4 cell count from baseline and at any given point of time there was no difference in the rate of increase of CD4 count between the two treatment arms (p=0.58). Our findings are comparable to that of other studies. In 2NN study the nevirapine twice daily and efavirenz group showed median rise of 160 cell/cm³. Although overall treatment failure was numerically lower in the efavirenz group than in the nevirapine-only groups, their findings don’t show evidence that efavirenz is superior to nevirapine twice daily in terms of treatment failure, but they could not show equivalence within the 10% limits of these treatment groups even though the study was adequately powered for such an analysis.22

In SENC (Spanish efavirenz vs. nevirapine comparison) trial and Italian Cohort Naive Antiretrovirals (I.Co.N.A.) study immunologic response was nearly same in NVP and EFV arms.20,21 Manfredi R et al in their study found limited immunologic advantage of EFV over NVP to 3 months only, when the mean increases of CD4 cell count vs. baseline level reached >40% for efavirenz and 25% for nevirapine. But it was not maintained thereafter until 18 months.27

Hypersensitivity reaction (6.6% in NVP vs. 2.32% in EFV, p=0.0146) and hepatitis (3.2% in NVP vs. 0% in EFV, p=0.0085) were more common with nevirapine, while neurologic disturbances (0.93% in NVP vs. 20.15% in EFV, p=0.0001) were more common with efavirenz. Incidence of distal sensory neuropathy and lipid abnormalities was similar in both the groups. Thus our findings are comparable to that of other studies.

### Table 2: Adverse drug reactions

<table>
<thead>
<tr>
<th>Side effects</th>
<th>NVP (n=857)</th>
<th>EFV (n=254)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>28(3.2%)</td>
<td>0 (0%)</td>
<td>0.0085</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>57(6.6%)</td>
<td>6(2.32%)</td>
<td>0.0146</td>
</tr>
<tr>
<td>CNS disturbances</td>
<td>8(0.93%)</td>
<td>51(20.15%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipid abnormalities</td>
<td>78(9.10%)</td>
<td>25(9.84%)</td>
<td>0.3606</td>
</tr>
<tr>
<td>Distal sensory neuropathy (clinical)</td>
<td>149(17.38%)</td>
<td>54(21.21%)</td>
<td>0.190</td>
</tr>
</tbody>
</table>

Fig. 1: CD4 cells response in both groups.

Fig. 2: Box plot nevirapine and efavirenz arm.

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The low frequency of skin rash in our study as compared to others was probably due to strict adherence to lead-in dose. Frequency of hepatitis was also low, that is because we screened the patients only when clinically indicated. Asymptomatic hepatitis may have been missed and CD4 cell count at the time of start of therapy was <250/cmm. None of our patient died because of hepatitis. Assessment of hepatitis virus co-infection was not done in all the patients so we couldn’t assess the effect of co-infection on incidence of hepatitis. So in resource poor settings performing liver function tests selectively may be enough and repeated screening may not be required. CNS side effects of efavirenz were generally mild and none of our patient required drug discontinuation.

Limitations of our study were non-randomization and lack of virologic data. Viral load test was not carried out due to financial constrain but immunologic benefit was seen suggesting adequate viral suppression.

In conclusion, our observational non-randomized study showed comparable immunological responses of NVP and EFV based HAART in antiretroviral naïve HIV 1 infected patients, with more rash and hepatotoxicity with NVP and CNS side effects with EFV. In developing countries like India nevirapine is a good alternative to efavirenz with comparable immunologic effectiveness. Side effect profile must be kept in mind while choosing any NNRTI based regimen.

REFERENCES