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## RESEARCH ARTICLE

# EVALUATION OF SECOND LINE ART DRUGS IN THE MANAGEMENT OF HIV-2 CASES ATTENDING ART OPD IN GOVERNMENT MEDICALCOLLEGE AND HOSPITAL, AURANGABAD

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**ABSTRACT**

**Background :** HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase (NNRTI) drugs, Nevirapine and Efavirenz, the mainstay of national first line ART regimen.[1] Studies mention that there is no clearly accepted regime for the management of HIV-2 .
**Aim of study:** To study the response to second –line ART drugs (as prescribed by NACO) in the HIV-2 cases attending ART center of tertiary care hospital.
**Method:** It is a cross- sectional study. Of the 12906 HIV cases registered in the ART Center of this institute, 16 cases are HIV-2 cases. In the present study, though the clinical profile of all the 16 has been reported, only 8 of the 16 who have been receiving treatment for more than a year have been studied for response to second line ART. Rise in CD 4 count, weight gain and rise in hemoglobin was calculated and statistical test of significance was applied.
**Results:** There was significant rise in CD4 count (p value of 0.007) and significant gain in weight (p value of 0.015), while change in hemoglobin before and after therapy was not significant.
**Limitations**: As reliable viral load measurement is not yet available for HIV-2infection,[1] the patients' response has to be judged clinically ,by rise in CD 4 count and weight gain.
**Conclusion:** After statistical analysis, it was observed that there was a significant rise in CD4 count and weight gain after one year of second line therapy. None of these patients developed new opportunistic infections.



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## INTRODUCTION

In 1986, the first case of HIV-2 was isolated from an AIDS patients in West Africa, in 1987 in the United States and in 1991 in India, respectively. Both HIV-1 and HIV-2 have the same modes of transmission and are associated with similar opportunistic infections and AIDS.However, 1) In persons infected with HIV-2, immunodeficiency seems to develop more slowly and cases are milder. 2) Compared to HIV-1, those with HIV-2 are less infectious early in the course of infection. 3) Vertical transmission of the virus is much less common. Parent-to-child transmission is only about 4%, including through breast feeding, 4) Nevirapine or Efaverinz are ineffective in HIV-2 infection. 5) Reliable viral load measurement is not yet possible for HIV-2 infection, hence the patients response has to be judged clinically and by CD4 counts (Omobolaji *et al*., 2011).

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Universally accepted treatment guidelines are not available (http://www.aidsmap.com/HIV-2/page/1322993/). In India, confirmatory tests started being carried out as a routine in referral laboratories like NARI (National AIDS Research Institute) in 2013. HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase (NNRTI) drugs, Nevirapine and Efavirenz. The options available for first –line HIV-2 treatment are the second line drugs for HIV -1,i.e. Nucleoside reverse transcriptase inhibitors, NRTIs- zidovudine, lamivudine, tenofovir or abacavir, or boosted protease inhibitors (PI- based) regimes, using saquinavir, lopinavir, darunavir, or indinavir. Boosted PI regime has been suggested by the U.S. department of Health and Human services (Omobolaji *et al*., 2011).

Triple drug regimens using NRTIs have been recommended by WHO earlier, but have been found to be rather unsuccessful (Thushan de Silva, 2010). Brower *et al* and Desbois *et al.* have found that Lopinavir, Saquinavir and Darunavir are potent inhibitors of HIV-2 protease in isolates. Atazanavir is not that effective[1,.]. In the Government set-up, the regimen prescribed

by NACO i.e .second-line ART is used. We studied the response to treatment of HIV-2 positive patients with this regimen, after they had received it for a year or more.

**Subjects and Methods**

This study was conducted in the ART plus center of this institute after Institutional Ethics Committee approval .Patients presenting to ICTC are subjected to 3 rapid tests, of which the second picks up HIV-2 positivity. This has to be confirmed by Western Blot for HIV-2 and PCR, that is performed in Maharashtra at NARI (National Aids Research Institute), Pune. When a case tests positive for HIV-2 in ICTC, he is referred to ART center, from where this case is referred to NARI. Fresh blood sample is drawn at NARI, and the report handed to the patient, who returns to the referring ART center. All HIV-2 cases who are confirmed by NARI, attending ART OPD, were included in the study. As on 30 June, 2015, the total number of HIV cases registered in ART center Aurangabad since 15 July, 2006 are 12,906 out of which only 16 patients were confirmed HIV-2. Verbal consent was taken. Confidentiality is strictly maintained.

If the CD4 count is more than 350 and the patient is in clinical Stage 0 or1 (no opportunistic infections etc.), he is registered as a pre ART case and called every 6 months for follow –up (or earlier if he has any symptoms). Otherwise he is registered for second line ART and given a month's quota of medicines after thorough counseling. Drugs Used in the ARTC as per NACO guidelines for HIV-2 management are: Tenofovir 300mg + Lamivudine 300 mg + Lopinavir 200 mg + Ritonavir 50 mg. The 16 registered cases of HIV-2 were studied clinically, with fresh CD4 counts, weight record and hematological investigations. The cases are under regular follow–up of our ART plus center. HIV status of spouses and offspring was recorded. Improvement or deterioration in general well-being, weight, CD4 counts, hemoglobin, new opportunistic infections, side effects of drugs, adherence were considered for evaluation of therapy. The parameters of weight, hemoglobin and CD4 count were subjected to statistical analysis, comparing the values before starting therapy and the current values, after completing minimum one year of treatment. (student t test , SPSS.)

## RESULTS

10 of the 16 HIV-2 cases were males (62.5 %). The maximum number of cases were in the age group of 31 to 50 years (11 out of 16 ,i.e.68.75%). The oldest patient was a 67 year old female and the youngest was a 33 year old male. Table 1.

**Table 1. Demography**

| Age group | Male | Female | Total | Percentage |
|---|---|---|---|---|
| 31 TO 40 | 2 | 3 | 5 | 31.25 % |
| 41 TO 50 | 5 | 1 | 6 | 37.5 % |
| 51 TO 60 | 3 | 0 | 3 | 18.75 % |
| 61 TO 70 | 0 | 2 | 2 | 12.5 % |
| Total | 10 | 6 | 16 | 100 % |

Out of 16 patients registered, the spouses of 5 are reported to be positive for HIV. Of these, 4 died of AIDS related complications and we do not have information about whether they had HIV 1 or HIV-2infection. One of the spouses who is registered as a pre – ART case, has HIV-2 infection. (Table 2)

**Table 2. Spouse status**

| | Positive | | Negative | | Not known | Total |
|---|---|---|---|---|---|---|
| | Live | Dead | Live | Dead | | |
| Spouse | 2 | 4 | 10 | 0 | 0 | 16 |
| Total | 6 | | 10 | | 0 | 16 |

**Table 3. Response to treatment**

| S. No. | Rise in CD from baseline | Weight Gain | Change in Hb |
|---|---|---|---|
| 1 | 507 | 5kg | 0.8 |
| 2 | 805 | 2kg | -0.2 |
| 3 | 172 | 15kg | -1.3 |
| 4 | 115 | 4kg | -0.4 |
| 5 | 189 | 9kg | -1.3 |
| 6 | 61 | 4kg | 1.6 |
| 7 | 293 | 2kg | -0.8 |
| 8 | 342 | 15kg | -1.6 |

**Table 4. Response to treatment**

| Average weight gain | Average rise in cd 4 count | Average change in haemoglobin count |
|---|---|---|
| 4 Kg | 310 | 0.4 Gm (Decreased) |

None of the off-spring (total 36) of the cases are HIV positive For studying the response to treatment, the 8 patients who have been taking ART for at least one year were analyzed for rise in CD4 count, weight gain and hemoglobin. The remaining 8 cases in whom treatment has been started only a few days or weeks ago have not been included in this analysis. In the 8 cases studied, all showed a rise in CD4 count. The average rise (difference between the CD4 count just before starting treatment and the current CD4 count) was 310 cells/$mm^3$ (p value 0.007)' The maximum rise was 805 cells/$mm^3$, the minimum was 61 cells/$mm^3$. All the 8 patients gained weight .The average gain was 4 kg (p value 0.015), the maximum being 15 kg and the minimum 2 kg.

These values are statistically significant. However, the mean hemoglobin decreased by 0.4 gm% (not significant, p value of 0.098). Table 5. All the 8 patients had a sense of well being and showed good adherence to the treatment. Table 3, Table 4.

None of the 8 patients developed any new opportunistic infections (OI), though all had some or the other OI earlier. In fact 7 of the 8 patients had OIs at the time of diagnosis which cleared after ART was started (3 had candidiasis, 3 chronic diarrhea and 1 had pulmonary tuberculosis as their initial presentation). Of the remaining 8 patients in whom treatment has recently been started and are not included in the statistical analysis, 4 were diagnosed when they presented with extra pulmonary TB, and 4 with chronic diarrhea. 1 of the cases who came with pleural effusion this time had herpes zoster opthalmicus in 2007. He initially received treatment with first line HIV drugs as confirmation of diagnosis of HIV-2 was not possible and second line drugs were not available in the Government setup those days.

**Table 5. Paired Samples Test**

| | Paired Differences | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | 95% Confidence Interval of the Difference Lower | Upper | | | |
| Weight Before Weight After | -8.00000 | 5.95219 | -12.97616 | -3.02384 | -3.802 | 7 | .007 |
| CD4 Before CD4 After | -289.00000 | 253.89593 | -501.26231 | -76.73769 | -3.219 | 7 | .015 |
| HbBefore Hb After | .53750 | .79810 | -.12973 | 1.20473 | 1.905 | 7 | .098 |

**Table 6. Opportunistic Infections**

| Opportunistic infection | Past | Current | Total |
|---|---|---|---|
| TB Pulmonary | 2 | 0 | 2 |
| TB extra-Pulmonary | 1 | 3 | 4 |
| Candidiasis Oral | 3 | 0 | 3 |
| Candidiasis Oesophageal | 1 | 0 | 1 |
| Chronic diarrhea | 7 | 0 | 7 |
| Herpes Zoster | 1 | 0 | 1 |

## DISCUSSION

Drugs used in the ARTC as per NACO guidelines in HIV-2 management are Tenofovir 300mg + Lamivudine 300 mg + Lopinavir 200 mg + Ritonavir 50 mg. In this study it was observed that there is significant rise in CD4 count and weight gain after initiation of second line ART as per NACO guidelines in cases of HIV-2 positive patients after at least one year of therapy. The general well-being also improved in all the cases. Opportunistic infections that were present in the past were resolved after the initiation of therapy in patients who had received second line ART for more than a few months. This study confirms the utility of second line drugs as per NACO guidelines in HIV-2 management. In this study, the average time taken for a case to be diagnosed, to the start of treatment, is 2 years 4 months. During this period, the patient was on pre ART observation or on first line drugs. The longest gap is of 6 years 7 months. In 6 of the 16 cases, treatment was started immediately after the patient was confirmed to have HIV-2 from reference lab (NARI) either because he was in stage 3 or 4 or his CD4 count was <350. 12906 cases have been registered in this ART center since July 2006 to June 2015 however, only 16 have been diagnosed to be HIV-2 (0.123 %).

This shows how uncommon the infection is in our region (which includes 14 districts) We do not have any case who has dual (HIV-1 and 2) infection nor any case in the paediatric age group. Our prevalence is lower than most other studies, perhaps because we have not included cases detected by screening tests, but only by confirmatory investigations. Centre of Excellence, JJ hospital Mumbai reports a prevalence of 149 out of 42,961 clients tested for HIV antibodies using rapid screening tests (0.35%) (Agrawal, 2010). The reason for this higher prevalence may be because all the patients from Maharashtra who were put on second line ART were referred to Mumbai till 2013. SACEP .in 4 other places has started since only 2013. Also, rapid screening tests may give falsely higher values. Murugan and Anburajan observed a prevalence of 0.29% of HIV-2 infection in south Tamil Nadu. Soloman *et al.* observed a prevalence of 0.8% of HIV-2 among urban population and 0.3% among rural population in Tamil Nadu. The modes of transmission for HIV-2 are the same as those for HIV-1 HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase (NNRTI) drugs, Nevirapine and Efavirenz. The options available for first –line HIV2 treatment are the second line drugs for HIV-1. Nucleoside reverse transcriptase inhibitors, NRTIs- zidovudine, lamivudine, tenofovir or abacavir or boosted protease inhibitors (PI- based) regimes, using saquinavir, lopinavir, darunavir, or indinavir.

Boosted PI regime has been suggested by the U.S. department of Health and Human services.[1]Triple drug regimens using NRTIs have been recommended by WHO earlier, but have been found to be rather unsuccessful. (HIV2 goes Global, 2010) Brower *et al.* and Desbois *et al.* have found that Lopinavir, Saquinavir and Darunavir are potent inhibitors of HIV-2 protease in isolates. Atazanavir is not that effective.Experts favor the use of 2 NRTIs like tenofovir with lamivudine or emtricitabine. Plus a ritonavir boosted PI. (Omobolaji, 2011) The ANRS CO5 HIV-2 Cohort assessed treatment response in 29 HIV2 positive individuals in whom lopinavir /ritonavir with NRTI showed improvement in CD4 count over 2 years in 20 patients. In these, HIV-RNA became undetectable too. Limitation of study 1.As viral load measurement is not yet available for HIV-2 infection in Government setup, response to treatment was assessed clinically, by rise in CD4 count and weight gain 2. Number of cases is less (16).

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