DOI: 10.7860/JCDR/2018/30700.11294

Original Article

Internal Medicine Section

Antiretroviral Therapy under the National Program: Experience of a Single Large Centre in Southern India

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ABSTRACT

Introduction: The National Aids Control Organization (NACO) has been providing free Antiretroviral Therapy (ART) in India since 2004. Several concerns exist regarding functional outcome, possible low rates of treatment adherence, treatment failure, mortality and high drug toxicity with the provision of large scale free ART.

Aim: This study was done to evaluate the outcomes of ability to return to work, lost to follow up rates, treatment failure and drug toxicity requiring regimen change from the ART centre located in Christian Medical College, Vellore, Tamil Nadu, India, which is a large tertiary care centre attached to an academic Infectious Disease and medical unit in Southern India.

Materials and Methods: A prospective longitudinal follow up study on patients enrolled in the NACO ART centre at a large tertiary care hospital in Southern India between April 2008 and April 2012 were followed up for a minimum of two years. Outcomes assessed were WHO clinical stage and functional status at the end of the follow up period, rate of lost to follow up, failure of ART, mortality rate and drug toxicity requiring change of regimen.

Results: There were 963 patients included in the study with a mean follow up period of 39.78 months (SD 11.34). At the end of the follow up period, 914 (94.9%) of the patients were asymptomatic (WHO clinical stage 1T) and 92.3% of all patients on treatment were able to return to work after ART initiation. We found low rates of lost to follow up (3.2%), drug toxicity and mortality (5.8%) compared to data from other centres in India. A total of 136 adverse events were recorded, the most common being Zidovudine induced anaemia (7.2%). There was also a very low rate of treatment failure in our cohort.

Conclusion: This data shows the overall success of the program and the feasibility of having low rates of lost to follow up because of rigorous methods used in follow up of patients and support offered by attachment to an academic infectious disease unit.

Keywords: Human immunodeficiency, Outcome assessment, Patient, Virus

INTRODUCTION

India ranks third among the nations with the largest number of people living with HIV infection [1]. The NACO rolled out its free ART program in 2004. Since then more than 810,000 people have received free ART through the program. High rates of lost to follow up, lack of adherence, treatment failure and toxicity have been reported when ART is provided in a large-scale program [2,3]. This study was done in a single large centre attached to a teaching hospital to evaluate the ART program with respect to proportion who returned to work, transfer out, lost to follow up, mortality, failure rates and drug toxicity. These are hard outcomes that can be used to determine the overall success of programmatic interventions.

MATERIALS AND METHODS

We conducted a prospective longitudinal follow up study of all patients initiated on Highly Active Anti Retroviral Therapy (HAART) at the ART centre in our institution in Vellore between 2008 and 2012. This ART centre is attached to a large private run medical college. The antiretroviral drugs are provided by the NACO and patients are treated as per the guidelines of the NACO [5].

Inclusion criteria: All patients enrolled for free ART between April 2008 and April 2012.

Exclusion criteria: none.

ART was initiated on all patients according to the NACO guidelines, which recommended ART initiation at a CD4 count of ≤200-cells/μl (2007-2012) and then subsequently CD4 ≤350-cells/μl or in WHO clinical Stage 3 or 4 disease [4,5]. Follow up was done by monthly evaluation at the centre. Follow up was done till December 2012. The study was approved by the Institutional Review Board of the Christian Medical College, Vellore and informed consent of patients was taken at the time of enrollment. Data were collected from patient records as entered by the medical officer employed at the centre.

Primary outcome assessed was the number of patients who were alive and able to return to work after HAART initiation. Secondary outcomes assessed were (i) the number of patients who were lost to follow up (defined as patients who did not come to collect drugs at the centre for a duration of three months or more), (ii) treatment failure (defined as patients who needed a switch of the entire ART regimen from first line to second line due to loss of antiviral efficacy identified by clinical and/or immunological criteria and referred to the State Clinical Experts Panel clinic for regimen change), (iii) mortality and (iv) significant drug toxicity requiring a substitution/ switch of drugs. Substitution refers to replacement of a single anti retroviral drug due to toxicity, intolerance or drug interactions. Switch refers to change of the entire antiretroviral regimen to a second line regimen.

STATISTICAL ANALYSIS

Data were analysed using mean, median, percentages and standard deviation using SPSS version 16.0 Confidence intervals 95% were calculated for main outcomes. Missing data were not analysed.

RESULTS

A total of 963 patients who were enrolled in the program since April 2008 were followed up for a mean duration of 39.78 months (SD 11.34).

Baseline Characteristics of Patients [Table/Fig-1,2]

The ratio of males to females enrolled at the centre was 1.8:1. About 78.6% of the patients enrolled were between the ages of 15 and 45. About 60% of the patients had WHO clinical Stage 3 or 4 HIV infection. About 29.1% of the patients were asymptomatic or had WHO stage 1 infection. The most common opportunistic infection in our cohort was disseminated tuberculosis with 29.7% of patients being infected. The other common opportunistic infections were oral candidiasis (7.2%), pulmonary tuberculosis (6.1%), pneumocystis jiroveci pneumonia (3.5%), diarrhea due to opportunistic pathogens (3%) and cryptococcal meningitis (2.4%). The majority of the cohort was not co-infected with Hepatitis B virus (96.3%) and had a negative serology for syphilis (97.9%). 50.2% of the patients were initiated on a regimen containing Zidovudine, Lamivudine and Nevirapine (AZT+3TC+NVP). Patients who had a significant anaemia at baseline (Hb<10 gm%) were started on a Stavudine based regimen with Lamivudine and Nevirapine (29.7%). Patients who were on concomitant anti-tuberculous therapy or those with liver disease were initiated on an Efavirenz based regimen with either Zidovudine or Stavudine. About 11.3% of the patients were on a regimen containing AZT+3TC+EFV (Zidovudine+Lamivudine+Efavirenz) and 8.9% were on a regimen containing d4T+3TC+EFV (Stavudine+Lamivudine+Efavirenz). CD4 counts at baseline were available for 924 patients. The median CD4 count of the patients at baseline was 149 cell/µl (IQR 151.75).

Variable	Subgroups	Number (Percentage)
Age	<15	31 (3.2)
	15-45	757 (78.6)
	>45	175 (18.2)
Sex	Male	616 (64.0)
	Female	347 (36.0)
Clinical stage	1	280 (29.1)
	2	105 (10.9)
	3	210 (21.8)
	4	368 (38.2)
HBsAg*	Positive	27 (3.7)
	Negative	712 (96.3)
VDRL*	Positive	16 (2.1)
	Negative	734 (97.9)
ART regimen	AZT+3TC+EFV	108 (11.3)
	AZT+3TC+NVP	483 (50.2)
	d4T+3TC+EFV	86 (8.9)
	d4T+3TC+NVP	286 (29.7)
Mean CD4 count at baseline		149 cells/µL

[Table/Fig-1]: Baseline characteristics.
*The remaining patients had missing data (either blood not given or test done elsewhere and reports not available)
AZT+3TC+EFV- Zidovudine+Lamivudine+Efavirenz
AZT+3TC+NVP- Zidovudine, Lamivudine and Nevirapine
d4T+3TC+EFV- Stavudine+Lamivudine+Efavirenz
d4T+3TC+NVP- Stavudine+Lamivudine+Nevirapine

OI	No. of patients (%) n=626
Disseminated TB	186 (29.7)
Oral candidiasis	45 (7.2)
Pulmonary TB	38 (6.1)
Pneumocystis jiroveci pneumonia	22 (3.5)
Chronic diarrhoea	19 (3)
Cryptococcal meningitis	15 (2.4)
NonHodgkin's lymphoma	7 (1.1)
Oesophagealcanidiasis	5 (0.8)
Toxoplasmosis	5 (0.8)
CMV	4 (0.6)
Genital herpes	3 (0.5)
Oral Hairy Leukoplakia	3 (0.5)
Disseminated mycosis	2 (0.2)
AIDS cholangiopathy	1 (0.2)
Invasive CA cervix	2 (0.3)
HIV encephalopathy	1 (0.2)
Recurrent bacterial infections	1 (0.2)

[Table/Fig-2]: Opportunistic diseases in patients pre-art.
The total in the table is 359. The remaining 267 patients did not have any opportunistic infection or malignancy; data were missing for 337 patients. It is possible that they did not have any opportunistic disease as well.

Outcomes

Primary outcome of patients [Table/Fig-3]: The proportion of patients who returned to work after HAART initiation was 92.3% (759) (95% CI: 90.3-94.1). Only 0.1% of the patients were bed bound even after being on ART for at least one year.

Performance status	No. of patients n=822	% (95%CI)
Working	759	92.3 (90.3%-94%)
Alive but not working	62	7.5 (5.9%-9.6%)
Bed bound	1	0.1 (0.01%-0.8%)

[Table/Fig-3]: Performance status of patients at follow up.
In the remaining 141 patients we did not have data about performance status at the end of the study.

Secondary outcomes: After initiation of ART, 5% (48) (95% CI: 3.7-6.6) of the patients were transferred to other centres, 3.2% (31) (95% CI: 2.3-4.6) were lost to follow up, 4.4% (42) (95% CI: 3.2-5.9) of the patients died within first six months after ART initiation and 1.4%(13) (95% CI: 0.08-2) died after the first six months. Mortality during the first 6 months is usually due to opportunistic diseases present before initiation of antiretrovirals [6].

Only 4.7% (46) (95% CI: 3.6-6.3) were referred to the State AIDS Clinical Experts Panel (SACEP) for second line ART following clinical and immunological failure.

Adverse drug reactions: There were 136 adverse reactions to ART seen in this period amongst 963 patients that were followed up. The most common adverse reaction was anaemia secondary to Zidovudine use which was seen in 8.2% (72) of the patients. The other frequent adverse events were rash secondary to Nevirapinein 2.3% (22), symptomatic hyperlactatemia 2.2% (19), peripheral neuropathy 2.1% (17), pancreatitis 0.3% (3), lipodystrophy 0.2% (2) and hepatitis 0.1% (1). About 13.7% of the patients required a drug substitution due to side effects.

Other performance outcomes: At follow up 94.8% (780) (95% CI: 93.2-96.3) were asymptomatic (WHO clinical stage 1T). Only 1.7% (14) had WHO clinical Stage 3T infection and 3.4% (28) remained clinical Stage 4T after a minimum of one year of ART.

The mean increase in CD4 count after at least one year of ART was 212 cells/µL.

DISCUSSION

The success of the AIDS control program in a developing country such as India is evident by the large number of patients detected, counselled and initiated on free ART. However, many concerns have been raised about high rates of lost to follow up and deaths with program based ART. There were concerns regarding large number of adverse events requiring regimen change as NRTI based drug regimens are known to be associated with significant adverse effects including anaemia and mitochondrial toxicity [2].

Evaluation of program effectiveness in other ART centres in India under the National AIDS control programme have shown that there are high rates of treatment drop outs and poor mechanisms of

follow up of these patients [3,7,8,9]. Also studies done on patients receiving Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) based HAART regimens in Botswana have shown high rates of treatment failure [10]. Treatment failure occurs as a result of treatment attrition.

In our cohort there was a very low rate of lost to follow up (3.2%) as compared to a 14-22% lost to follow up rate in other cohorts [7,8,9,11]. The good clinical outcomes, with >90% of patients being able to work and low rates of lost to follow up were primarily because of the rigorous methods of patient follow up employed at the centre. If patients did not arrive on time get their prescriptions refilled they are telephoned and a post card reminder sent. If patients did not respond to these reminders they were visited at home. Homelessness, being single, young (age <25) and illiterate have been shown to be associated with increased rates of lost to follow up [7]. Probably the follow up methods employed at our centre ensured treatment compliance despite these factors. The overall mortality rate in our cohort (5.8%) is also relatively low compared to 12% in a smaller cohort of patients studied in Pune and 29 per 100 person years in another cohort from Jharkhand [3,12]. The increased early death rate (<6 months) was due to opportunistic infections diagnosed prior to HAART initiation including tuberculosis, Pneumocystis jiroveci pneumonia, chronic diarrhea and cryptococcal meningitis. The adverse event rates were similar to the Pune cohort [3] but were much lower than the Delhi cohort (14% vs. 30%) [10]. Only, 4.7% of the cohort was referred for second line anti retrovirals due to treatment failure. This was comparable to the experience of other cohorts [13].

This study is able to demonstrate the success of the free ART program beyond doubt and establish the efficacy of the first line antiretroviral regimens employed with fairly low rates of toxicity. Data from our cohort shows that it is possible to maintain very low rates of program attrition through rigorous methods of patient follow up. This was possible at our ART centre because of the unique partnership between an academic institution and the government. The presence of highly motivated staff and social workers who maintained contact with patients, conducted home visits and inputs from an academic Medicine and Infectious disease department contributed to the very low attrition rates. This unique model of private public partnership at the Christian Medical College, Vellore may offer lessons for the large scale ART program in India and other countries.

LIMITATION

1. The outcomes measured were as per the existing NACO operational guidelines. There were no additional tools employed to assess the quality of life of patients on Antiretroviral therapy.
2. The exact cause of death was not ascertained, as the study was not designed to do so.

CONCLUSION

The free antiretroviral therapy program in a developing country like India has enabled a large majority of HIV infected patients to resume a normal active life with very few adverse effects. Patient adherence to medication can be achieved by rigorous follow up using highly motivated staff ensuring the overall success of the program.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 05, 2017**
Date of Peer Review: **Jul 13, 2017**
Date of Acceptance: **Nov 17, 2017**
Date of Publishing: **Mar 01, 2018**