

Antiretroviral therapy outcome in human immuno-deficiency virus infected patients in a tertiary care hospital

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ABSTRACT

Background: Human immunodeficiency virus (HIV) presently accounts for the highest number of deaths due to any infective agent in the world. The present study assessed the one year treatment outcome following antiretroviral therapy in HIV positive, treatment naïve patients in a tertiary care hospital.

Methods: Adult HIV positive, antiretroviral treatment naïve patients who were started on antiretroviral therapy (ART) between 1st January 2011 and 31st May 2013 were included in the study. Data was collected from their case records. CD4+cell count, haemoglobin level, weight, occurrence of opportunistic infections (OIs) and adverse drug reactions (ADRs) were analysed at baseline, 6 and 12 months following start of antiretroviral therapy. Data was analysed using parametric and nonparametric tests.

Results: Data of 325 patients was analysed. Overall, the median increase in CD₄⁺ count at 1 year after initiation of treatment was observed to be clinically significant. Patients on tenofovir based regimen showed a significantly greater increase in the median CD₄⁺ count ($P = 1.12 \times 10^{-05}$) and haemoglobin ($P = 0.002$) as compared to those on non-tenofovir based regimen. A total of 151 ADRs were recorded in the study, of which the most common were skin rash 24%, anaemia and gastrointestinal side effects 17% each. Frequency of opportunistic infections gradually declined after ART. At the end of 1 year of treatment, the cumulative loss to follow up was 7.4%.

Conclusions: By following the current national guidelines, the desired immunological and clinical response following initiation of ART can be achieved while minimizing drug toxicity.

Keywords: Antiretroviral therapy, Clinical outcome, Tenofovir, Nontenofovir

INTRODUCTION

Human immunodeficiency virus (HIV) currently accounts for the highest number of deaths due to any single infective agent in the world. As per data in March 2013, there are 18.13 lakh people living with HIV/AIDS in India with around 1.16 lakh new HIV infections among adults every year.¹

As per NACO 2013 guidelines, all HIV infected patients with a CD₄⁺ count of ≤ 350 cells/mm³ or those with WHO clinical stage 3 or 4 irrespective of CD₄⁺ count should be initiated on ART.¹ The regimen selected is based on their efficacy, side effects, drug availability, cost, potential drug interactions, comorbidities, opportunistic infections (OIs), and need for laboratory monitoring.² Current guidelines indicate that initial ART should contain an NNRTI (either nevirapine-NVP or efavirenz-EFV) plus two NRTIs, one of which should be zidovudine (AZT) or tenofovir disoproxil fumarate (TDF) and the other lamivudine (3TC) or emtricitabine (FTC).²

Cost of the drug as well as the cost of monitoring the patients, management of adverse drug reactions, drug substitution and change of regimens also affects selection of a drug. Thus, comparing agents in terms of outcome during routine patient care is useful for policy makers regarding ART selection.³⁻⁵ Some studies have assessed survival, morbidity and medication adherence among Indian patients receiving ART in the private and non-governmental sectors.³⁻⁵ This study examined treatment outcomes in terms of immunological improvement, improvement in weight and haemoglobin, occurrence of opportunistic infections and adverse reactions using routinely collected ART data from the tertiary care hospital setting. Further, a nonrandomized comparison study of TDF with other commonly used nucleoside reverse transcriptase inhibitors based regimens was undertaken.

Objectives

Primary objective

To assess the change in CD₄⁺ cell count following one year of antiretroviral therapy in treatment naïve HIV positive patients.

Secondary objectives

1. To study the one year outcome of antiretroviral therapy with respect to change in hemoglobin and weight in treatment naïve patients.
2. To assess and compare treatment outcome and adverse drug reaction (ADR) profile between patients on tenofovir versus those on non-tenofovir based antiretroviral regimen.

METHODS

A prospective cohort study was conducted from September, 2012 to August, 2014 at a tertiary care hospital in South India, after obtaining approval from Institutional Ethics committee. The study data was collected from the case records of patients in the HIV clinic and medical records department. HIV positive patients (>18 years of age) who were treatment naïve and started on antiretroviral therapy (ART) as per the national guidelines, between 1st January 2011 and 31st May 2013, were included in the study. The data related to one year follow up following start of ART was collected. Patients demographics, antiretroviral regimen initiated, drug substitution and change of regimen was noted. CD₄⁺ cell count, haemoglobin level, weight, occurrence of opportunistic infections (OIs) and adverse drug reactions (ADRs) were analysed at baseline, 6 and 12 months following start of antiretroviral therapy.

Statistical analysis

A descriptive approach was used for data analysis. The results were expressed as percentage. Changes in CD₄⁺ cell count, haemoglobin level and weight were analysed in terms of the median change between baseline and follow-up measures at 6 and 12 months. Independent samples t-test was used to compare mean baseline values (age, weight and haemoglobin) between groups. Mann-Whitney U test/two-sample Wilcoxon signed rank test was performed to compare medians of continuous variables between groups (change in haemoglobin, change in weight and change in CD₄⁺ count). Fisher's exact test was conducted to determine the significant difference between groups for count data (No. of patients with OIs/ADRs). P<0.05 was considered statistically significant.

RESULTS

Demographic profile

Baseline demographic, clinical and immunological characteristics of 325 patients initiated on antiretroviral therapy (ART) has been illustrated in Table 1.

Treatment outcomes

Change in weight and haemoglobin levels during follow up

Patients improved clinically with regard to weight and haemoglobin levels during the 1-year treatment period. At the end of 12 months, the median increase in haemoglobin was 1.5 g/dL (IQR 0.7-2.5) and the median weight gain was 3 kg (IQR 1-6, n=325) (Table 2).

CD₄⁺ changes during follow up

The median increase in CD₄⁺ count at 1 year was 158 cells/mm³ (IQR 124-205; n=154) (Table 2). It increased

by 50-100 cells/mm³ in 4 (1.2%) patients and more than 100 cells/mm³ in 150 (46.2%) patients.

ART regimens used

The tenofovir (TDF) based regimens used were TDF (tenofovir)+3TC/FTC (lamivudine/emtricitabine) + EFV/NVP (efavirenz/nevirapine). The non-tenofovir based regimens used were AZT (zidovudine) + 3TC (lamivudine)+NVP/EFV (efavirenz/nevirapine); d4T (stavudine)+3TC (lamivudine)+NVP/EFV (efavirenz/nevirapine) and ddl (didanosine)+3TC (lamivudine)+NVP (nevirapine) .

Table 1: Baseline demographic, clinical and immunological characteristics of 325 patients initiated on antiretroviral therapy.

Characteristics	n* (%)
Age in years	n* (%)
18-30	29 (8.9)
31-45	144 (44.3)
> 45	152 (46.8)
Employment	n (%)
Employed	231 (71)
Gender	n (%)
Male	232 (71.4)
Female	93 (28.6)
Marital status	n (%)
Married	292 (89.8)
Opportunistic Infections	n (%)
At least one before start of ART	222 (68.3)
Weight (Mean ±SD)	52.9±9.1 kg
Haemoglobin (Mean±SD)	11.5±2 g/dl
CD ₄ ⁺ count (Median) [IQR]	96 (52-231) cells/mm ³

n=no. of patients; value in parentheses are percentages unless otherwise stated

Occurrence of opportunistic infections (OI)

During the 1-year treatment period, 11.1% of patients (36/325) had one or more OIs (Table 2). The frequency of OIs was highest in the initial months of treatment and declined sharply thereafter. The cumulative proportion of patients who reported an OI after start of treatment at 6 and 12 months was 8.9% and 11.1% respectively. After the start of treatment, mucosal candidiasis (n=55; 16.9%) was the most common OI reported, followed by cryptococcal meningitis (n=15; 4.6%). The others were pulmonary tuberculosis (n=14), *Pneumocystis jiroveci* pneumonia (n=7), disseminated tuberculosis (n=6) and TB lymphadenitis (n=3).

Adverse drug reactions (ADRs)

During the 1-year treatment period, 40% of patients (130/325) reported ADRs (Table 2). Of a total of 151 side-effects reported, the most frequent were skin rash

(24%), anaemia (17%), gastrointestinal adverse effects (17%), peripheral neuropathy, pancreatitis and renal failure (8% each). The occurrence of side-effects was not significantly associated with baseline weight.

Table 2: Treatment outcomes of 325 patients following initiation of antiretroviral therapy.

Characteristics	At 6 months	At 12 months
Change in Hb (Median) (IQR)	0.5 (0.4-1.3) g/dL	1.5(0.7-2.5) g/dL
Change in weight (Median) (IQR)	1 (0-4) kg	3 (1-6) kg
Change in CD ₄ ⁺ count (Median) (IQR)*	90 (63-128) cells/mm ³	158 (124-205) cells/mm ³
No. of patients with ADR n (%)	-	130 (40%)
No. of patients with treatment substitution n (%)	50 (15.4%)	90 (27.7%)
No. of patients with OIs after start of ART n (%)	29 (8.9%)	36 (11.1%)
No. of patients loss to follow up n (%)	-	24 (7.4%)
Cumulative no. of patients died n (%)	1 (0.3%)	4 (1.2%)

*n=154; patients with missing values, those died, loss to follow up, treatment failure cases confirmed by HIV RNA load and those who stopped drugs either due to side-effects or missed to take were excluded from analysis.

Regimen

Thirty-five per cent of patients were started on AZT+3TC+NVP while 31% started on TDF+FTC+EFV. Among 90 of the 325 patients, one of the drugs in the regimen had to be substituted during the 1-year treatment period (Table 2).

Loss to follow-up and mortality

Of the 325 adults started on ART, treatment outcomes were available for 301 patients over 1 year; of these, 297 patients were alive after 1 year of treatment. The cumulative loss to follow-up at 12 months after ART initiation was 7.4% (24/325) (Table 2). Overall, 4 (1.2%) of the 325 patients died during one year. Over the 1-year period, in 57 (17.5%) patients the prescribed monthly drugs were either stopped due to side-effects or the patient failed to take the drugs on at least 1 occasion. Adherence to treatment was reported in 229 (70.2%) patients. Treatment failure was confirmed by HIV RNA load test in 11 (3.4%) patients at the end of 1 year. In this study, data regarding HIV RNA was not included for analysis (except in 11 patients to confirm treatment

failure), as majority of patients refused to take the test due to cost involved in testing.

Comparison of patients on tenofovir based versus those on non-tenofovir based regimens

Comparison of baseline characteristics between two groups

There was no significant difference in baseline characteristics between the two groups (Table 3).

Table 3: Comparison of demographic and baseline characteristics between tenofovir and non-tenofovir based regimens.

Characteristics	Tenofovir based regimen	Non-tenofovir based regimen	
No. of patients	143 (44%)	182 (56%)	
Sex			
Male	108 (75.5%)	124 (68.1%)	
Female	35 (24.5%)	58 (31.9%)	
Age (Mean + SD)	44±11 years	47±12 years	
Weight (Mean+SD)	52.3±8.9 kg	53.43±9.2 kg	P = 0.270*
Haemoglobin (Mean +SD)	11.27±2.1 g/dL	11.6±1.8 g/dL	P = 0.139*
CD4 ⁺ count (Median) (IQR)	85 (43-250) cells/mm ³	113 (61-231) cells/mm ³	P= 0.754**
No. with opportunistic infection before start of ART n (%)	104 (72.7%)	118 (64.8%)	

*Independent samples t-test, **Mann Whitney U test, n=number of patients

Comparison of treatment outcomes between two groups

There was no significant difference in median change in weight and haemoglobin between the two groups. Neurological side-effects were most commonly reported by patients started on a stavudine (d4T)-based regimen (11, 7%), anaemia by those on AZT-based regimen (24, 16%) and renal failure in (12, 8%) patients on tenofovir based regimens. Patients on tenofovir based regimen were less likely to develop an adverse drug reaction (ADR) and experience an OI than those on non-tenofovir based regimen (Table 4). The commonly used non-tenofovir based regimen was AZT+3TC+NVP. Of the 114 patients started on AZT+3TC+NVP, the regimen was changed to TDF+3TC+EFV in 12 (34%) and to AZT+3TC+EFV in 11 (31%). The commonly used tenofovir based regimen (100 patients) was TDF+FTC+EFV which was changed to AZT+3TC+NVP in 8 of them.

Table 4: Comparison of treatment outcomes at the end of 1 year between tenofovir and non-tenofovir based regimens (total number of patients=325).

Characteristics	Tenofovir based regimen (n = 143)	Non-tenofovir based regimen (n = 182)	
Change in Hb (Median) (IQR)	1.8 (1-2.7) g/dL	1.2 (0.6-2.1) g/dL	
Change in weight (Median) (IQR)	4 (1-6) kg	3.4 (1-6) kg	P= 0.825**
Change in CD4 ⁺ count(Median) (IQR)*	175 (136-205) cells/mm ³	144 (115-211) cells/mm ³	P = 1.12×10 ⁻⁵ ***
Patients with ADR	33 (23.1%)	97 (53.3%)	OR = 0.26
Patients without ADR	110 (33.8%)	85 (26.2%)	P= 3.35×10 ⁻⁰⁸ ***
Regimen frequently used for substitution	AZT+3TC+NVP 8 (5.6%)	TDF+FTC+EFV 20 (11%)	
No. of patients with OIs after start of ART	10 (7%)	26 (14.3%)	OR=0.99 P=1***
No. of patients loss to follow up	8 (5.6%)	16 (8.8%)	
No. of patients died	1 (0.7%)	3 (1.7%)	

*n = 154; patients with missing values, those died, loss to follow up, treatment failure cases confirmed by HIV RNA load and those who stopped drugs either due to side-effects or missed to take were excluded from analysis **Two-sample Wilcoxon signed rank test; ***Fisher's exact test

DISCUSSION

A majority of patients were above 45 years of age and the proportion of males was more than two-fold greater than the females. This is consistent with another study in Indian scenario wherein there was a predominance of males.¹⁶ This study data showed that women had a higher median CD4⁺ cell count at baseline. This was because most of them who had acquired the infection from their HIV- positive spouse were diagnosed before any symptom manifestation.

Almost half of the patients presented late for treatment with poor baseline parameters such as baseline CD4⁺ count less than 100 cells/mm³ and presence of opportunistic infections. This finding points to the need for rapid scale-up of counselling and testing for early detection of asymptomatic cases in developing countries.

This study is also consistent with the results of Bolton-more et al, that patients starting a zidovudine-based regimen or nevirapine-based regimen were considerably more likely over time to have that drug substituted, compared with patients starting a tenofovir-based regimen or efavirenz-based regimen respectively.^{11,13} It was observed that the NACO recommended first-line regimens are fairly well tolerated and associated with adherence rates comparable with those in the United States.¹⁷

Almost fifty per cent of the patients in the cohort experienced a more than doubling of his or her CD₄⁺ cell count in the first 12 months of ART. The CD₄⁺ cell response is generally vigorous for treatment naïve patients on ART. Here in this study, CD₄⁺ lymphocyte count gains were impressive and are similar in magnitude at 1 year on treatment to those reported elsewhere, in spite of the relatively late initiation of treatment.^{14,18,19}

New pulmonary infections occurring while patients are receiving ART are well diagnosed in this setting. The study also showed a gradual decline in the presence of OIs following ART. New reports of OI during the follow-up period reduced with treatment.

Definitive evidence regarding the relative efficacy of various treatment strategies can only be gathered through randomized clinical trials. Information about the same in controlled conditions in different patient population should be obtained to check if results are similar. The findings in our study shows the effect of the introduction of tenofovir based regimens as first-line regimen by the treating physician as established in clinical trials.^{7,10} This effect was maintained when subgroup analyses comparing tenofovir and non-tenofovir based regimens was performed. The comparison was done based on the baseline characteristics and treatment outcomes between the two groups. This was possible as the vast majority of subjects in the study received initial therapy with a regimen containing either tenofovir or zidovudine.

Rate of treatment change due to adverse events were uniformly low, and comparable or lower than those published for other cohorts.^{9,20} This demonstrates that with standardized regimens, and monitoring, ART can be safely used in resource-constrained settings. The most common indication resulting in a treatment change was in patients who developed tuberculosis after starting ART and who were switched from nevirapine to efavirenz, due to concerns about the co-administration of nevirapine with rifampicin.

Unlike other published reports, here only four deaths were found during one year follow-up of patients.^{7,15,21,22} Though the specific cause of death could not be ascertained, it was found that three of them had a baseline CD₄⁺ count of less than 100 cells/mm³. Mortality could be further avoided by monitoring those with advanced disease as they start ART, and it raises the possibility that

early mortality could also be due to undiagnosed opportunistic infections, nutritional deficiencies, or severe immune reconstitution inflammatory syndrome, although there is no direct evidence to support these possible reasons.²³⁻²⁵

This study showed reduced early mortality as patients who attended the clinic were diagnosed quickly and were counselled to start ART before they become wasted and anemic.⁶ Though the stigma associated with the disease prevent patients from seeking early treatment, the free provision of drugs by government ART centres has encouraged people to seek medical attention earlier, as has been observed in the United States and other developed countries.⁸

Adherence to medication and lifestyle changes is a key factor to positive treatment outcome in the therapy of HIV/AIDS and this presents a challenge to both patients and healthcare providers.^{12,26-30} Our patients were counselled on the basic facts about ART before and after treatment initiation.

Despite these and the fact that all the respondents were counselled on medication adherence before starting ART, adherence was still found to be poor, 70.2% (229), compared to the 100% recommended level of adherence required to achieve the goal of ART. The data was collected from case records as reported by patients. This is consistent with a recent study of self-reported poor adherence (<80%).²⁰ The various reasons for non-adherence could be busy working schedule, pill burden, cost, lack of understanding of how to take drugs, etc.

Although this study has not sought to explore the costs of treatment, HIV RNA testing is expensive relative to drug costs. This highlights the need for lower cost of HIV RNA testing together with antiretroviral drugs, or of validating approaches that do not include HIV RNA testing.

Strengths of this study include the intent-to-treat analysis, and complete follow-up for 93% of the cohort.

The principal limitation of the analysis is the short duration of follow-up and the small numbers at risk in the analysis of those on 1 year of treatment. The results of this study are, however, comparable with data from observational settings in both developed and developing countries. This study builds on results reported for other Indian settings in demonstrating the feasibility of successful ART centres in these contexts.³¹⁻³⁴

As this was an observational study, there wasn't a control group and hence treatment outcome for every patient was assessed by comparing the pre-ART CD₄⁺ cells counts and CD₄⁺ cells counts while on ART. Fluctuations in absolute CD₄⁺ count do occur requiring repeated measurements to make a definite conclusion, but that was not the case with this study.³⁵ The actual causes of death

could also not be ascertained. There were cases of missing or incomplete records with regard to recording of side-effects and follow up measurements of clinical and immunological parameters that hampered the study. Some aspects of data collection were based on self-report, which could be biased. Thus, the frequency of side-effects reported may be underestimated and the reported clinical and immunological improvements may be biased towards a higher value.

The results remained statistically significant after adjusting for presence of OI, CD₄⁺ cell count, sex, and age at baseline. These findings provide encouragement to physicians seeking to provide similar services in poor communities where HIV morbidity and mortality are high.

CONCLUSION

By following the current national guidelines, the immunological and clinical outcome of ART while minimizing adverse drug reactions during the first year of treatment, did not differ from those in developed countries.

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