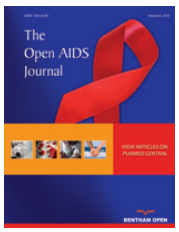

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RESEARCH ARTICLE

Long-Term Impact of First-Line Anti-Retroviral Therapy on HiV-1 Positive Patients: A Retrospective Study in Karnataka, India

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Abstract:

Purpose:

In resource-limited settings like India, the treatment efficacy of ART is monitored through CD4 count and clinical indicators. The objective of this study is to assess outcomes and indicators of treatment failure in patients on long-term first-line ART.

Methods:

We carried out a retrospective study using data from 851 patients collected from ART centers established in two tertiary care hospitals of Kasturba Medical College, Mangalore. All HIV-1 positive patients initiated on first-line therapy from 2001 to 2009 were monitored.

Results:

Of the 851 patients, 62.6% were males, median age was 37 years and 90% were infected through heterosexual contact. About 21% of the total patients surveyed were reported to have died, 2.5% withdrew treatment, 2.5% were transferred out and 1.5% were lost to follow up. Moreover, 11.2% of the population were reported to have switched to second-line therapy due to poor adherence (p=0.0001). Of those evaluated for failure (n=95), 36.8% were due to both immunological and virological failure, and 34.7% were due to virological failure. Median CD4 count at initiation was 260 cells/mm^3, while the median recent CD4 count was 555 cells/mm^3. In our study, an association between adherence with outcome was found to be statistically significant.

Conclusion:

To conclude, this study proves that better adherence led to a favorable long-term outcome.

Keywords: CD4 count, Adherence, HIV, India, Viral load, ART.

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1. INTRODUCTION

It has been over 4 decades since the world has been battling with HIV's alarming pandemic. As of 2019, more than 38 million people in the world are living with HIV, out of which only 25.4 million are receiving access to antiretroviral therapy [1]. In India, as of 2017, people living with HIV are roughly 2.1 million, making it the country harbouring the third largest HIV population in the world.

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According to the India HIV Estimation report of 2017 [2], prevalence of adult (15-49 years) HIV is estimated to be 0.22% (0.16%-0.30%) in 2017. Among males, the prevalence is estimated at around 0.25% (0.18%-0.34%) and at 0.19% (0.14%-0.25%) among females. The incidence of adult HIV in India has fallen from an estimated peak of 0.38% in 2001-03 through 0.34% in 2007, 0.28% in 2012 and 0.26% in 2015 to 0.22% in 2017. This decrease is attributed to the swift expansion of ART access in the country.

The ultimate aim of ART is to restore the immune system by causing successful viral suppression, which will in turn halt onset and progression of the disease as well as reduce

susceptibility to opportunistic infections.

Anti-retroviral therapy (ART) began its course with the introduction of the first nucleoside reverse transcriptase inhibitor – Zidovudine back in 1987, which turned out to be effective in prolonging survival, although the duration was later proven to be limited. Following this, the first Protease inhibitors– Saquinavir, Ritonavir and Indinavir in the year 1995, were introduced.

Since its establishment in 1987, India has been under National AIDS Control Organisation (NACO), aiming to provide easy access to anti-retroviral drugs to those plagued by the deadly virus. While the initial goal of this program was to reach out to a vast majority of individuals living with HIV in India and to initiate them on ART, thereby significantly reducing morbidity and mortality, the final aim is to ensure the excellent long-term quality of life. Several studies assessing short-term outcomes in patients undergoing treatment with first-line ART have been done, but data regarding outcomes of first-line ART over long periods of time are relatively scarce in India.

India, being a resource-limited setting (RLS), monitors treatment efficacy through immunological markers such as CD4 count and clinical indicators (WHO staging).

Hence, this long-term retrospective study aims to investigate the survival and continuous indicators of treatment failure in patients on routine ART services following initial viral suppression.

2. MATERIALS AND METHODS

This study was conducted in two tertiary care hospitals of Kasturba Medical College Hospital, in Mangalore, Karnataka, India. These hospitals witness patients from all over Karnataka, including nearby states like Kerala, Tamil Nadu, *etc*.

It is a retrospective study. The study population included 851 samples of HIV-1 positive patients who initiated therapy with first-line ART from 2001 to 2009. Their CD4 count was regularly monitored and their data was followed up till 2019. Of the 851 patients who initiated treatment from 2001-2009, only 617 patients were evaluated for indicators of failure since the remaining were either lost to follow up, died, transferred to a different facility or withdrew treatment and hence, no further data was available for those patients.

All those aged 2 years and older, diagnosed with HIV-1 who have undergone or are undergoing treatment with first-line ART from 2001 to 2009 were included. Any HIV-1 positive patient with the duration of treatment with first-line less than 10 years was excluded.

Archival data were collected from folders of patients registered under the ART Centre of Kasturba Medical College, Mangalore. Pertinent information, such as social demographics, regular CD4 counts, ART regimen, current comorbidities, associated opportunistic infections, WHO grade and adherence pattern were noted. Details regarding viral load testing were recorded from a few patients for whom the testing was done.

Statistical Package for Social Sciences (SPSS) version 20 was used to analyse the data. Descriptive statistics like mean, proportions and standard deviation were used for expressing the results. The association between various clinical characteristics and outcome was analysed using Chi square test for the categorical variable and independent sample t-test and Mann-Whitney test for continuous variables wherein $P < 0.05$ was considered significant.

Approval for the study protocol was obtained from the Institutional Ethics Committee of Kasturba Medical College, MAHE, Mangalore, India preceding the initiation of the study. After gaining approval from the committee, permission was obtained from the Head of the Institution and Hospital Authorities to carry out the study.

Baseline demographics (age, sex, educational level, occupation, marital status, mode of transmission, year of enrollment and site of enrollment) and clinical variables (first-line ART regimen, current ART regimen, date and reason for shift to second-line therapy, body mass index (BMI), CD4 cell count, baseline WHO clinical stage, viral load and adherence patterns) were evaluated.

While analyzing, categorical variables were used for each factor based on quartiles and occupation was divided into employed (laborers, government/private service, professionals) and unemployed (which includes students, homemakers, and retirees). BMI was grouped into four categories defined by WHO: obese (≥30.0), overweight (≥25.0), normal (18.5-24.9 kg/m^2), and underweight (<18.5kg/m^2).

We used WHO criteria [3] to define the following variables for failure:

Clinical criteria- After 6 months of effective treatment in adults and adolescents, a new or recurrent clinical event suggests severe immunodeficiency (WHO clinical stage 4). New or recurrent clinical event in children after 6 months of effective treatment suggests advanced or severe immunodeficiency (WHO clinical stage 3 and 4 with the exception of TB).

Immunological failure- CD4 levels persistently below 100 cells/mm^3 for adults and adolescents, persistently below 200 cells/mm^3 in children less than 5 years and consistently below 100 cells/mm^3 in children more than 5 years.

Virological failure- Two consecutive viral load measurements show values above 1000 copies/mL after 3 months, with adherence support.

Treatment for any patient was considered to have failed if they met any of these criteria.

Adherence to the drug regimen for each patient was calculated using standard NACO [4] guidelines for adherence monitoring. The following formula was used:

$$\text{Percentage of adherence} = \frac{Number\ of\ pills\ given - Number\ of\ pills\ balance}{Number\ of\ pills\ should\ have\ taken}\ x\ 100 \quad \textbf{(1)}$$

3. RESULTS

Out of the 851 individuals who commenced treatment with first-line therapy from 2001-2009, 179 (21%) patients were reported to have died, 21 (2.5%) withdrew treatment, 21 (2.5%) were transferred out and 13 (1.5%) were lost to follow

up. Data for those who died, were lost to follow up, shifted to a different facility, or opted out were not available and hence were not included in the analysis.

From the remaining sample of patients (n=617) for whom data was readily available, they were divided into two groups: treatment responders (n=522) (still continuing on first-line therapy after 10 years of follow-up) and non-responders [n=95] (those who shifted to second-line therapy at or after 10 years of treatment with first-line).

From amongst those who were recruited for first-line therapy from 2001-2009 (n=851), 533 (62.6%) were males, mean age was 37 years (±11.829; Range: 2-78) and 647 (90%) were infected through heterosexual contact. Most of them were unemployed [135 (15.9%)], while 386 (45.4%) were educated at the primary level, 434 (51%) patients were married, and 200 (23.5%) were single. CD4 count for each patient was evaluated serially till 48 months and the most recent count measured was noted. Mean baseline CD4 count was 260 cells/mm^3 (±230.69) whilst the mean of the most recent CD4 count was 555 cells/mm^3 (±244.05). At treatment initiation, 293 (34.4%) patients were started on Zidovudine, Lamivudine and Nevirapine-containing regimen and 159 (18.7%) on Stavudine, lamivudine and Nevirapine-containing first-line regimen. While only 10 (1.1%) were started on Tenofovir-containing regimen.

Among those on current ART regimens, the majority [358 (42.1%)] were on Zidovudine, Lamivudine and Nevirapine containing regimen, followed by Tenofovir, Lamivudine and Efavirenz containing regimen [116 (13.6%)].

The percentage of the population who was reported to have switched to second-line therapy was 11.2% (n=95). Of those evaluated for failure, 35 (36.8%) were due to both immunological and virological failure, 33 (34.7%) were due to virological failure, and 19 (20.0%) patients were reported to have only immunological failure.

Average adherence of the samples was 93.7% (±7.631). Among the 95 patients who changed to second-line treatment after being on first-line for 10 years, their mean baseline CD4 count was 246.42 cells/mm^3 (±203.02), mean baseline viral load was 16722.6 copies/mL (±37340.7). Mean viral load at the time of switch was 96,817 copies/mL (±175294.3).

Viral load testing was done in only 33 patients, wherein, the mean baseline viral load was 14556.12 copies/mL (±34719.2).

Table **1** intended to find a correlation between baseline characteristics (sex, age, marital status, educational level and occupation) of the population included in the study [n=617] and the outcome of treatment. Association between age and outcome of treatment was found to be mildly significant (p=0.049), indicating that younger age groups were showing better treatment outcomes.

From Table **2**, we deduce that there is no association between BMI and baseline CD4 count of the patient and the outcome of treatment (p=0.764 and p=0.294, respectively).

We were able to find a statistically significant association between the mean CD4 count of the patient population with adherence (p=0.006). It was noted that better adherence (>95%) correlated with higher mean CD4 count values (Table **3**).

Table 1. Baseline characteristics of the patient population.

Characteristics	Total	Responders	Non-responders	P value
Age (years)	n=617 (%)	n=522 (%)	n=95 (%)	
<40	429 (69.5)	362 (69.3)	67 (70.5)	0.049
≥40	188 (30.4)	160 (30.7)	28 (29.5)	
Sex	n=617 (%)	n=522 (%)	n=95 (%)	
Male	364 (58.9)	306 (58.6)	58 (61)	0.362
Female	253 (41.0)	216 (41.3)	37 (38.9)	
Occupation	n=617 (%)	n=522 (%)	n=95 (%)	
Employed	419 (67.9)	353 (67.6)	66 (69.4)	0.982
Unemployed	198 (32.1)	169 (32.4)	29 (30.6)	
Marital Status	n=617 (%)	n=522 (%)	n=95 (%)	
Married	348 (56.4)	304 (58.3)	44 (46.3)	
Widowed	104 (16.8)	89 (17.0)	15 (15.8)	0.339
Single	155 (25.1)	121 (23.3)	34 (35.7)	
Divorced	10 (1.7)	8 (1.5)	2 (2.2)	
Educational level	n=617 (%)	n=522 (%)	n=95 (%)	
Illiterate	44 (7.1)	37 (7.0)	7 (7.4)	
Primary School	320 (51.8)	265 (50.7)	55 (57.8)	0.585
Secondary School	203 (32.9)	176 (33.7)	27 (28.4)	
College and above	50 (8.1)	44 (8.4)	6 (6.3)	

Table 2. Clinical and Immunological Characteristics of the patient population.

BMI (kg/m^2)	Responders [n=522 (%)]	Non-responders [n=95 (%)]	P value
<18.5	141 (27)	28 (29.4)	0.764
18.5-24.99	266 (50.9)	52 (54.7)	
25.0-29.99	101 (19.3)	11 (11.5)	
>30	14 (2.6)	4 (4.2)	
CD4 count at baseline (cells/mm^3)			0.294
≤100	132 (25.2)	26 (27.3)	
101-200	130 (24.9)	21 (22.1)	
201-350	128 (24.5)	23 (24.2)	
≥350	129 (24.7)	25 (26.3)	

Table 3. Association between mean CD4 count and adherence (p=0.006).

Adherence (%)	n	Mean CD4 count (cells/mm^3)	Standard deviation	P value
<95	313	538.99	245.08	0.006
>95	299	573.19	242.15	

Similarly, from Table **4**, a strong association was found between outcome of treatment and adherence of the patients. Those with higher adherence (>95%) were found to be continuing with first-line ART whilst those who had lower adherence (<95%) switched to second-line treatment (p=0.0001).

Table 4. Association between outcome and adherence of treatment (p=0.0001).

Adherence (%)	Responders [n=522 (%)]	Non-responders [n=95 (%)]	P value
<95	246 (47.1)	76 (80.0)	0.0001
>95	276 (52.8)	19 (20.0)	

4. DISCUSSION

This is one of the first studies conducted in Karnataka, India involving a long-term evaluation of both adult and paediatric patients on first-line ART. The study aimed to assess the determinants that led to treatment failure in those receiving long-term first-line anti-retroviral therapy. A total of 851 individuals who initiated anti-retroviral therapy between 2000 and 2009 were followed up till 2019 and relevant parameters were analysed. Owing to that fact that India belongs to a resource-limited setting, routine viral load testing, which is a standard practice in developed countries, began only recently in India. Prior to this, indicators like clinical (WHO grade, BMI, *etc*) and immunological (CD4 count) markers were used to monitor and assess treatment failure. Hence, this study primarily focuses on those markers to evaluate the outcome of long-term treatment with first-line ART.

Our data showed that majority of patients, during the early years of enrolment, were initiated on d4T-containing regimens, which was later replaced with AZT-containing regimens due to increased incidence of unpleasant side-effects. Eventually, the latter was also replaced by TDF-containing regimen due to a change in treatment guidelines.

In a study conducted by Jemberu Nega *et al.* [5] in Ethiopia, it was shown that poor adherence was related to both virological and immunological failure. This finding was the highlight of our study, and we were able to demonstrate a strong association between adherence and treatment outcomes (Table **4**), (p=0.0001) [6].

According to studies conducted in Shenzen, China by Peng Huang *et al.* [7] and in Kenya by Musa Otieno *et al.* [8], patients with higher baseline WHO and lower baseline CD4 count had a higher probability of undergoing immunological failure. Our study showed no such association (Table **2**). The study conducted in China by Peng Huang *et al.* [7] also implicated that older age was a significant risk factor for treatment failure, which is similar to our study (Table **1**) (p=0.049). This finding can be attributed to the pattern of declining immunity with increasing age, which can alter the response to treatment and can be a major factor responsible for failing first-line ART. Therefore, early diagnosis and prompt initiation with ART should be a must. This is in contrast to studies conducted by Seema *et al*. in Nigeria [9] and by Amin Hassan *et al.* in Kenya [10], which showed that younger age is a strong risk factor for treatment failure.

Despite patients experiencing treatment failure, immunologically or virologically, mortality rate was relatively low [(21%) n=170]; thereby corroborating the fact that good adherence led to great outcomes in the form of undetectable viral load, high CD4 counts and a good quality of life.

Lack of routine viral load testing in the last decade impairs our ability to use this gold standard method of assessing treatment efficacy to study trends of failure. Although immunological and clinical markers can be used to evaluate when to initiate treatment and monitor progress, studies [11] have shown that they have low sensitivity and specificity and should only be used secondary to viral load in determining treatment outcomes. Therefore, it is crucial to expand the usage of testing viral loads so it can be used as the primary variable in further studies.

Particular limitations to the study, like missing data, rendered us unable to assess more variables that could possibly contribute to treatment failure, such as side-effects to treatment and associated addictions, which could have been one of the reasons for the switch to the second line. No data was available for those who were lost to follow up (LTFU), transferred to a different facility or opted out, which could have been a contributing factor in undermining the mortality rate. Tests detecting resistance to drugs were not done due to high cost.

CONCLUSION

Through this 10-year study, we were able to conclude that first-line ART is very effective and is well-tolerated. Factors associated with treatment failure were poor adherence, and older age. Therefore, it is crucial to thoroughly investigate the cause of failure before making a switch to a higher generation of anti-retroviral therapy, and to avoid the emergence of drug

resistance. On the other hand, baseline CD4 counts, WHO grade and BMI were not shown to be statistically significant in predicting treatment failure.

AUTHORS' CONTRIBUTION

The study conception and design were contributed by all the authors. Material preparation and data collection were performed by Dr. Aishah Khan and Dr. Nikhil Victor D'Souza. Data analysis was performed by Dr. Ramesh Holla and Dr. Vaman Kulkarni. The first draft of the manuscript was written by Dr. Aishah Khan and Dr. Ramesh Holla. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Ethics Committee of Kasturba Medical College, Mangaluru.

HUMAN AND ANIMAL RIGHTS

The authors declare that all procedures performed in this study abide by the ethical standards of the institutional research committee.

CONSENT FOR PUBLICATION

Informed consent was obtained from the participants.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available in the ART centre of tertiary care hospitals of Kasturba Medical College, Mangalore, Karnataka.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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