Original Article

# A prospective study to evaluate efficacy of second-line antiretroviral therapy given to human immunodeficiency virus patients at Antiretroviral Therapy Plus Centre in India

Jigar P. Modi, Amita Kubavat[1], Shailesh Mundhava[1], Usha Lalwani[2]
Department of Pharmacology, B J Medical College, Ahmedabad, [1]Department of Pharmacology, P.D.U. Government Medical College, Rajkot, [2]Department of Pharmacology, GMERS Medical College and Hospital, Sola, Ahmedabad, Gujarat, India

**Address for correspondence:**
Dr. Usha Lalwani, Department of Pharmacology, GMERS Medical College and Hospital, Sola, Ahmedabad, Gujarat, India.
E-mail: ushalalwani89@gmail.com

## Abstract

**Introduction:** Despite a very large number of patients being covered under antiretroviral therapy (ART), there are limited data in the Indian population regarding second-line ART. Hence, this study was undertaken to evaluate the efficacy of second-line ART. **Materials and Methods:** After consultation with the physician of ART Plus Centre, the patient was interviewed, and details of patients' case record were obtained. In our ART Plus Centre, CD4 count has been done at the start and after 6 months of second-line ART which were recorded as effectiveness indicator of second-line ART. **Results:** Out of seventy patients, 16 (22.86%) had a history of second-line ART from private ART clinics and 54 (77.14%) patients were transferred from other government ART centers. The most common reason to start second-line ART was immunological failure in 27 patients. The mean increase in CD4 count of 106.09 cells/mm$^3$ was observed after 6 months of second-line ART in 63 patients. The mean increase in CD4 count (57.16%) after 6 months was statistically significant ($P < 0.05$) with tenofovir + lamivudine + atazanavir/ritonavir regimen in forty patients. **Conclusions:** Irrational practice by private hospitals limits treatment options, with increasing the chances of drug resistance. On the other hand, the National AIDS Control Organization-sponsored second-line ART was found to be effective as 84.12% of patients had improvement in their mean CD4 count.

**Key words:** CD4, efficacy, human immunodeficiency virus, second-line antiretroviral therapy

## INTRODUCTION

Human immunodeficiency virus (HIV) infection has been a growing challenge worldwide for the past three and a half decades. Since the first cases of acquired immunodeficiency syndrome (AIDS) were reported in 1981, infection with HIV has grown to pandemic proportions.[1]

Although antiretroviral therapy (ART) does not cure HIV infection, the decrease in the viral load and the improvement in immunological status brought about by the use of these drugs have resulted in a marked decrease in the mortality and morbidity associated with the disease.[2]

The advent of highly active ART has been a boon for HIV-infected patients by reducing the morbidity and

Access this article online

Quick Response Code:

Website: www.ijstd.org

DOI: 10.4103/ijstd.IJSTD_53_18



**How to cite this article:** Modi JP, Kubavat A, Mundhava S, Lalwani U. A prospective study to evaluate efficacy of second-line antiretroviral therapy given to human immunodeficiency virus patients at Antiretroviral Therapy Plus Centre in India. Indian J Sex Transm Dis 2019;40:51-6.

extending the lifespan.[3] However, with increasing exposure to first-line ART, the risk of viral resistance and subsequent treatment failure has become more important, and switching to second-line regimens is increasingly needed.[4] The WHO estimates that the average switch rate from first- to second-line ART is 2%–3% per year for adults.[5] In order to expand the access to second-line treatment, 37 "ART Plus" Centres were started and capacitated to provide second-line/alternative first-line treatment to eligible patients. Till September 2014, 10,223 patients received second-line ART drugs from ART Plus Centres.[5]

Antiretroviral treatment failure can be defined virologically, immunologically, or clinically and in most instances, one type of failure follows the other.[2] The National AIDS Control Organization (NACO) and the WHO have made certain guidelines to define immunological failure which includes definitions of decline in CD4 count after 6 months of first-line ART. Increase in CD4 count after 6 months of second-line therapy is one of the ways to assess its efficacy.

Despite a very large number of patients being covered under ART, there are limited data in Indian population regarding second-line ART. Therefore, the present study was undertaken to evaluate the efficacy of second-line ART in HIV-positive patients attending ART Plus Centre.

### Aim

To evaluate the efficacy of the second-line ART.

## MATERIALS AND METHODS

Prior permission of the Departmental Screening Committee of the Department of Pharmacology of the same institute, Institutional Ethics Committee of the same institute, Gujarat State AIDS Control Society, and National AIDS Control Society were obtained before the conduct of the study.

Patients selected on the basis of inclusion and exclusion criteria were explained in detail about this study. Written informed consent of all the patients was obtained before enrollment into the study as participants. Patients were explained about the nature of HIV infection, importance of ART, and adherence to ART during treatment.

In our ART Plus Centre, ART is usually provided for 30 days. The patient has to come after 30 days of the last visit to refill ART for the next month. At each encounter, the patient has to consult physician in charge of the ART Plus Centre. Line of management, ART, and other drug prescription were carried out by the physician. At our ART Plus centre, CD4 count has been done at the start and after 6 months of second-line ART as an indicator of second-line ART effectiveness.

### Data analysis

1. Reason to start second-line ART
2. WHO clinical stage of patients
3. CD4 count comparison at the start and after 6 months of second-line ART (as an indicator of second-line ART effectiveness).

### Statistical analysis

Recorded data were analyzed by Microsoft Office Excel 2013 and GraphPad Prism software version 6.

- Normal distribution of the study data was analyzed using D'Agostino–Pearson's omnibus test
- Wilcoxon matched-pairs signed-ranks test was applied on paired data of CD4 count at baseline and 6 months of second-line ART to analyze improvement in CD4 count.

## OBSERVATIONS AND RESULTS

### Distribution of patients based on the place of treatment at the start of second-line antiretroviral therapy

A total of 54 patients had started second-line ART from government ART Plus Centre. While 16 patients (22.86%) had started their second-line ART in private clinic, they were either referred or transferred to government ART Plus Centre.

### Reason to start second-line antiretroviral therapy

Out of seventy patients on second-line ART, 27 had immunological failure, whereas 19 patients had both immunological and virological failure and 8 patients had started second-line ART at a private hospital. In such cases, second-line ART was continued by ART Plus Centre to prevent treatment failure and resistance to drug regimens. In seven patients, immunological failure was observed who transferred from private hospitals, six patients had virological failure, whereas two had clinical failure [Table 1].

### Distribution of patients according to WHO clinical stage

At the start of second-line ART, 52 patients were categorized as WHO Stage I, whereas seven patients were categorized as Stage III and four patients as Stage IV. After 6 months of second-line ART, there was increase in patients who were categorized

as Stage I ($n$ = 56), whereas two patients were categorized as Stage II and one patient as Stage III. There was no change in the number of patients who were categorized as Stage IV [Table 2].

## CD4 count comparison at the start and 6 months of second-line antiretroviral therapy

As shown in Table 3a in this study, out of the seventy enrolled patients, 63 patients' CD4 count at 6 months of ART could be recorded. At the start of ART, 63.49% of patients had CD4 count of ≤200 cells/mm$^3$ and 36.51% of patients had CD4 count of >200 cells/mm$^3$. At 6 months of second-line ART, 34.92% of patients had CD4 count of ≤200 cells/mm$^3$, and 65.08% of patients had CD4 count of >200 cells/mm$^3$.

## Statistical consideration of CD4 count comparison at the start and 6 months of second-line antiretroviral therapy

Statistical analysis was carried out by GraphPad Prism software version 6. CD4 counts at the start and 6 months of second-line ART were assessed for their normal distribution using normality test. As data did not follow normal distribution, they were further analyzed using nonparametric test, Wilcoxon matched-pairs signed-ranks test ($P < 0.05$ was considered statistically significant). This showed that there is statistically significant improvement in CD4 count at 6 months in comparison to baseline CD4 count [Table 3b].

**Table 1: Reason to start second-line antiretroviral treatment ($n$=70)**

| Reason to start second-line ART | Number of patients (%) |
|---|---|
| Immunological failure | 27 (38.57) |
| Immunological + virological failure | 19 (27.14) |
| Transfer from private hospitals | 8 (11.42) |
| Immunological failure + transfer from private hospitals | 7 (10) |
| Virological failure | 6 (8.57) |
| Clinical failure | 2 (2.85) |
| Immunological + virological failure + transfer from private hospitals | 1 (1.42) |
| Total | 70 (100) |

ART=Antiretroviral therapy

**Table 2: Distribution of patients according to the WHO clinical stage**

| Time period | Number of patients with the WHO Stage | | | |
|---|---|---|---|---|
| | Stage I (%) | Stage II (%) | Stage III (%) | Stage IV (%) |
| Baseline ($n$=63) | 52 (82.54) | 0 (0) | 7 (11.11) | 4 (6.35) |
| At 6 months ($n$=63) | 56 (88.88) | 2 (3.17) | 1 (1.60) | 4 (6.35) |

**Table 3a: CD4 count comparison at start and 6 months of second-line antiretroviral treatment**

| CD4 count (cells/mm$^3$) | At start of ART ($n$=63) | At 6 months of ART ($n$=63) |
|---|---|---|
| ≤100 | 22 (34.92) | 3 (4.77) |
| 101-200 | 18 (28.57) | 19 (30.15) |
| 201-300 | 11 (17.46) | 18 (28.58) |
| 301-400 | 5 (7.93) | 6 (9.52) |
| 401-500 | 3 (4.77) | 8 (12.70) |
| >500 | 4 (6.35) | 9 (14.28) |

ART=Antiretroviral therapy

## Absolute CD4 count change (improvement/fall) at 6 months of second-line antiretroviral therapy

As shown in Table 3c, 53 out of the 70 patients (84.12) showed improvement in CD4 count, whereas in 10 patients (15.88%), a fall in CD4 count was recorded as compared to their baseline CD4 count. Majority of the patients, 68.23%, showed improvement in CD4 count up to 200 cells/mm$^3$, and 15.89% patients showed improvement in CD4 count of >200 cells/mm$^3$.

## Comparison of different second-line antiretroviral therapy regimens in improving CD4 count at 6 months of treatment

In this study, out of the 70 patients, 59 patients had completed 6 months of second-line ART regimen without any substitution. Out of all regimens, improvement in CD4 count at 6 months was statistically significant ($P < 0.05$) with tenofovir (TDF) + lamivudine (3TC) + atazanavir/ritonavir (ATV/r) (mean increase in CD4 count − 57.16%) and D4T + 3TC + ATV/r (mean increase in CD4 count − 56.17%) regimens, in comparison of other second-line ART regimens in which statistical test was not applied due to very less sample size. As all groups did not follow normal distribution nonparametrically, Wilcoxon matched-pairs signed-ranks test ($P < 0.05$ was considered statistically significant) was applied to compare difference in improving CD4 count [Table 3d].

# DISCUSSION

In this study, the most common cause for switching to second-line ART was immunological failure ($n$ = 27). One of the common causes for switching to second-line ART was combined immunological and virological failure (19 patients, 27.14%) followed by immunological failure plus shifted from private clinics where already second-line ART was started without following the NACO guidelines (seven patients, 10%). Six patients had virological failure at the start of therapy, whereas two

**Table 3b: Statistical consideration of CD4 count comparison at the start and 6 months of second-line antiretroviral treatment**

| Criteria | At the start of second-line ART (*n*=63) | At 6 months of second-line ART (*n*=63) | Mean difference | Percentage increase in CD4 count | *P* |
|---|---|---|---|---|---|
| Mean CD4 count | 190.52 | 296.61 | 106.09 | 55.68 | <0.05 (statistically significant) |
| SD | 166.59 | 171.36 | 4.77 | | |

SD=Standard deviation; ART=Antiretroviral therapy

**Table 3c: Absolute CD4 count change (improvement/fall) at 6 months of second-line antiretroviral treatment**

| Absolute CD4 count improvement (cells/mm$^3$) at 6 months of ART | Number of patients with improved CD4 (*n*=63) | Absolute CD4 count fall (cells/mm$^3$) at 6 months of ART | Number of patients with fall in CD4 (*n*=63) |
|---|---|---|---|
| 0-50 | 8 (12.70) | 0-50 | 5 (7.93) |
| 51-100 | 15 (23.80) | 51-100 | 2 (3.18) |
| 101-200 | 20 (31.73) | 101-200 | 2 (3.18) |
| 201-300 | 5 (7.94) | 201-300 | 0 |
| 301-400 | 2 (3.18) | 301-400 | 1 (1.59) |
| 401-500 | 2 (3.18) | 401-500 | 0 |
| >500 | 1 (1.59) | >500 | 0 |
| Total patients | 53 (84.12) | Total patients | 10 (15.88) |

ART=Antiretroviral therapy

**Table 3d: Comparison of different second-line ART regimens in improving CD4 count at 6 months of treatment**

| ART regimen | TDF + 3TC + ATV/r | D4T + 3TC + ATV/r | AZT + 3TC + ATV/r | AZT + 3TC + LPV/r | ABC + 3TC + ATV/r |
|---|---|---|---|---|---|
| Number of patients continued same initial second-line ART regimen till 6 months (*n*=59) | 40 | 11 | 4 | 2 | 2 |
| Mean±SD CD4 count (cells/mm$^3$) at the start of second-line ART | 190.20±184.51 | 156.81±74.41 | 319.25±137.85 | 275±364.86 | 162.00±182.43 |
| Mean±SD CD4 count (cells/mm$^3$) at 6 months of second-line ART | 298.92±171.40 | 244.90±83.06 | 480.25±212.93 | 334.50±355.67 | 176.00±36.76 |
| Mean increase in CD4 count (cells/mm$^3$) (%) | 108.72 (57.16)* | 88.09 (56.17)* | 161 (50.43) | 59.5 (21.63) | 14 (8.64) |

**P*<0.05 statistically significant. SD=Standard deviation; ART=Antiretroviral therapy; TDF=Tenofovir; ATV/r=Atazanavir/ritonavir; LPV/r=Lopinavir/ritonavir; ABC=Abacavir; 3TC=Lamivudine; D4T=Stavudine; AZT=Zidovudine

patients had clinical failure (2.85%). In our study, there was one patient who had immunological and virological failure with transfer from private hospitals. Out of the 70 patients, 16 patients had started second-line ART at private hospitals. According to the NACO, experience had shown that the private sector concurrently uses second-line ART drugs, such as abacavir and protease inhibitors (PIs) as first line, and this has resulted in a cohort of nonnaïve treatment-experienced patients.[6] Second-line ART was started in some patients without following the NACO guidelines by various private hospitals with a view to achieve rapid clinical improvement. Few patients were given drug regimens which include both first- and second-line ART in private hospitals. In such cases, second-line ART was continued by ART Plus Centre to prevent treatment failure and resistance to drug regimens. Such irrational practice by private hospitals limits treatment options with increasing the chances of drug resistance and mortality. All these factors increase the prevalence of second-line ART patients in the society. Similar study was conducted at a civil hospital, Ahmedabad, Gujarat, which shows that the most common cause for switching to second-line ART was combined immunological and virological failure (64 patients, 51%) followed by clinical plus immunological plus virological failure (44 patients, 35%).[7]

In this study as shown in Table 2, 52 patients were categorized as WHO Stage I at the start of the study, whereas seven patients were categorized as Stage III and four patients as Stage IV. After 6 months of second-line ART, there was increase in patients who were categorized as Stage I ($n$ = 56), whereas two patients were categorized as Stage II and one patient as Stage III. There was no change in the number of patients who were categorized as Stage IV after 6 months of ART. The number of patients with Stage III was reduced from seven at baseline to one. These findings suggest that treatment with second-line ART resulted in marked improvement in clinical condition of the patients in our study.

The WHO staging is an important parameter to diagnose clinical (treatment) failure. Our study observed that 82.54% of patients were in Stage I, i.e., asymptomatic at the time of enrollment. This finding indicates that clinical failure manifests at late stage and is a poor indicator to diagnose first-line treatment failure. Therefore, it is recommended that all patients on first-line ART should be monitored regularly by CD4 count and plasma viral load to detect the treatment failure at the earlier stage rather than relying entirely on clinical condition.

According to the NACO, second-line regimens should include at least three active drugs; one of them from a new class, in order to increase the likelihood of the success of the treatment and to minimize the risk of cross-resistance. The PI class should be reserved for second-line treatments. If zidovudine (AZT) is used in first-line, Nucleoside reverse transcriptase inhibitor choice in second-line could be TDF, whereas if TDF is used in first-line ART, NRTI's choice could be AZT. However, if both TDF and AZT cannot be used, the last option is D4T. The Thai national guidelines for ART also suggest that AZT or TDF in combination with 3TC is recommended as the preferred NRTI backbone.[8]

The CD4 cell count remains the strongest predictor of HIV-related complications, even after the initiation of therapy.[9] In this study, 63.49% of patients had baseline CD4 count of ≤200 cells/mm$^3$ and 36.51% of patients had CD4 count of >200 cells/mm$^3$. At 6 months of second-line ART, 34.92% of patients had CD4 count of ≤200 cells/mm$^3$ and 65.08% of patients had CD4 count of >200 cells/mm$^3$ [Table 3a]. In another clinical study with the same number of patients, distribution of CD4 count at the initiation of second-line ART was also observed, which shows that 54.3% of patients had CD4 count of <200 cells/mm$^3$ at baseline, whereas 50.7% of patients had CD4 count ≤200 cells/mm$^3$ after 6 months of second-line ART.[10]

The mean CD4 count at baseline was 190.52 cell/mm$^3$, and the mean increase in CD4 count of 106.09 cells/mm$^3$ was observed ($P < 0.05$, statistically significant) at 6 months of second-line ART [Table 3b], which shows that there was 55.68% of increase in mean CD4 count after 6 months of second-line ART. Various studies have been conducted across the world that also show good results in CD4 count rise after the administration of second-line ART [Table 4].

In this study, in 84.12% of patients, improvement in CD4 count at 6 months of second-line ART was observed in comparison to baseline CD4 count, whereas in 15.88% of patients, fall in CD4 count was observed [Table 3c]. CD4 count fall below pretherapy baseline level after initiation of ART therapy is considered immunological failure, as per WHO and national guidelines.[9]

In this study, 59 patients had completed 6 months of second-line ART regimen without any substitution. Out of all the regimens, improvement in CD4 count at 6 months was statistically significant ($P < 0.05$) with TDF + 3TC + ATV/r (mean increase in CD4 count −57.16%) and D4T + 3TC + ATV/r (mean increase in CD4 count −56.17%) regimens, in comparison of other second-line ART regimens in which statistical test was not applied due to very less sample size [Table 3d]. These differences may be due to less number of patients in these regimens; differential accumulation of resistance mutations; drug interaction with co-medications; or various patient-related factors such as concomitant disorders, clinical and immunological stage at initiation of ART, nutritional status of patient, and adherence to therapy.

In our setup, routine testing of HIV viral load was not available. Although it is a standard practice in high-income countries, determination of the HIV load is not recommended in developing countries because of the costs and technical constraints. The delay in the initiation of second-line ART regimen allows viral replication and immunological and virological deterioration. Various studies show that, in resource-limited settings, switching to second-line regimens tends to occur earlier and at higher CD4 cell counts in ART program with viral load monitoring compared with program without viral load monitoring.[12] Viral load testing can be an important guide for clinical decisions on when to switch from first-line to second-line treatment and how to optimize the duration of first-line treatment.[13] As CD4 cell count tests are

**Table 4: Comparison of CD4 count rise in different studies after 6 months of second-line antiretroviral treatment**

| Time period | Present study (*n*=70) | Mean increase in CD4 count (cells/mm$^3$) | | | |
|---|---|---|---|---|---|
| | | Patel *et al.*, 2013[7] (*n*=126) | Ferradini *et al.*, 2011[10] (*n*=70) | Pujades-Rodrı´guez M *et al.*, 2008 (*n*=370) | Fox and Rosen, 2010[11] (*n*=328) |
| 6 months | 106.09 | 163.5 | 80 | 90 | 63 |

comparatively simple and affordable, the WHO has advocated CD4 cell count as a basis for the identification of treatment failure in resource-limited settings.[14]

However, like any other study, there were few limitations.

First, it was an observational, single-center study.

Second, the viral load remains the most sensitive indicator of ART failure. Recognizing early failure facilitates the decision to switch drugs before multiple resistance mutations develop to drugs of the first-line regimen. In our setup, routine viral load testing is not available, so 6-month follow-up data were not available about viral load. The lack of viral load monitoring in resource-limited settings may lead to late switching of regimens, increase the risk of viral resistance, and jeopardize long-term prognosis.

Third, the patients were observed for 6 months. Considering the lifelong treatment of ART, long-term follow-up is necessary to establish continual clinical, virological, and immunological improvement.

## Acknowledgments

We would like to acknowledge medical officers and staff of ART Plus Centre who gave us full support and cooperation during this study.

## CONCLUSIONS

It can be concluded that NACO-sponsored second-line ART was found to be effective as 84.12% of patients had improvement in their mean CD4 count. There was a good compliance in majority of the patients with increase in mean CD4 count after 6 months of second-line ART. Further, research is needed with large sample size to determine if this early outcome can be sustained over the following years of treatment.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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