Original Article

# Characterization of human immunodeficiency virus-infected patients of suspected first-line antiretroviral treatment failure within 5 years – Evidence from a tertiary hospital, Kolkata

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## Abstract

**Objectives:** Antiretroviral therapy (ART) has immense survival benefit on human immunodeficiency virus (HIV)-infected people. However, every year, a proportion of patients were failing to the first-line drugs. The aim of this study is to characterize the patients developing first-line failure within 5 years of ART. **Materials and Methods:** A retrospective observational study was carried out at the Centre of Excellence in HIV care, School of Tropical Medicine, Kolkata. A total of 190 referred patients' data of suspected first-line treatment failure who failed first-line ART within 5 years of initiation were collected and analyzed using R software. **Results:** Among 190 patients, 100 (52.4%) patients had virologic failure. Male patients 78 (41.05%) outnumbered females 22 (11.57%) and needed to switch to the second-line drugs. The median age was 37 years (range 8–65 years), and the median duration of first-line ART taken was 2.85 years. Among the first-line failed patients, zidovudine, lamivudine, and nevirapine (23.6%) was the most common antiretroviral regimen and 77 (40.5%) referred in the WHO stage I of illness. Seventy-three (38.42%) patients were referred for immunological failure, 26 (13.7%) for both immunological and clinical failure, and only 1 (0.52%) had only clinical failure at the time of referral. We found a significant association of suboptimal adherence ($P < 0.05$) and high viral load in this study. **Conclusion:** This study enables that poor adherence was the most important factor responsible for the first-line treatment failure. As adherence is a dynamic process, interventions in every visit following ART initiation should be optimized, and a multidisciplinary approach toward adherence is needed to get the highest treatment outcome benefit.

**Key words:** Adherence, antiretroviral drugs, human immunodeficiency virus

## INTRODUCTION

The global effort toward the universal access to antiretroviral (ARV) drugs over the past three decades has resulted in substantial reductions in morbidity and mortality of people infected with human immunodeficiency virus (HIV) AIDS

Access this article online

Quick Response Code:

Website: www.ijstd.org

DOI: 10.4103/ijstd.IJSTD_81_18



**How to cite this article:** Modak D, Dutta N, Pain S, Ghosh (De) R, Guha SK. Characterization of human immunodeficiency virus-infected patients of suspected first-line antiretroviral treatment failure within 5 years – Evidence from a tertiary hospital, Kolkata. Indian J Sex Transm Dis 2019;40:159-64.

and also increased the life expectancy of those people.[1,2] In 2015, there were 2.1 million new HIV infections worldwide, adding up to a total of 36.7 million people living with HIV (WHO, 2016). India has demonstrated an overall reduction of 57% in estimated annual new HIV infections (among adult population) from 0.274 million in 2000 to 0.116 million in 2011, and the estimated number of people living with HIV was 2.08 million in 2011.[3] The adult HIV prevalence at national level has continued its steady decline from an estimated peak of 0.38% in 2001–2003 through 0.34% in 2007 and 0.28% in 2012 to 0.26% in 2015 National AIDS Control Organization (NACO). The proportion of patients on the second line in resource-limited settings is estimated between 1% and 5%. In India as per Technical Report 2015 published by NACO, a total of 300,743 HIV patients are on first-line antiretroviral therapy (ART) and NACO envisages that nearly 3000 patients have become resistant to first-line therapy and put on second-line ART4.[4] In India, 13.95% of patients had immunological failure that was in need of switching to a second-line regimen.[5] A growing proportion of patients is constantly developing resistance to first-line ART which is inevitable sooner or later and has switched to second-line regimens. Late switches of first-line regimens, which contain nonnucleoside reverse-transcriptase inhibitors (NNRTIs), are associated with the accumulation of mutation and lead to cross-resistance to other NNRTI drug that might be used as a second-line option.[6]

Several risk factors for treatment failure are described in different studies. Some of them were sociodemographic factors (e.g., age), baseline clinical factors (e.g., baseline CD4 count and WHO clinical stage), drug–drug interactions, drug side effects, drug toxicity, or inadequate adherence to treatment are some of the factors associated with treatment failure.[7] Viral load (VL) and CD4 T-cell counts are the most commonly used parameters to monitor the efficiency of ARV treatment.[8]

Routine HIV VL monitoring is the standard of care for persons receiving ART in developed countries, but in resource-constraint country like India, targeted plasma VL test is recommended by WHO to confirm treatment failure for persons who meet selected immunologic and clinical criteria. Almost all ARV management decisions for treatment failure are based on addressing virologic failure.

Hence, it is very crucial to detect treatment failure as early as possible to reduce overall morbidity and mortality. Little is known about factors that are responsible for treatment failure in Eastern India.

The aim of this study is to observe the characteristics of patients who had failed the first-line ARV drugs within 5 years of ART initiation.

## MATERIALS AND METHODS

### Study population

HIV-infected referred patients who satisfied the criteria of suspected first-line treatment failure according to the NACO guideline (either clinical and or immunological failure) and on first-line ARV drugs for 5 years or less, attended Centre of Excellence in HIV Care, STM, Kolkata, from respective ART centers for virologic confirmation were our study participants. We analyzed the recorded data of patients from linked ART centers for suspected treatment failure of the year 2013 and 2015 (January–December), respectively. As plasma VL estimation could not be done routinely for every suspected failure in 2014, we exclude the patient's data of 2014 from this study.

### Study design

It was a hospital-based retrospective cohort study conducted at the Center of Excellence STM, Kolkata. Data regarding patients' baseline characteristics and treatment-related information were collected through review of their medical formats (SACEP Registrar). All data are entered into Excel spreadsheets and were cleaned for outliers, and then data are imported to SPSS version 16.0, SPSS Inc, Chicago, IL, 2007 for statistical analysis. Simple descriptive statistics including the mean, median, range, percentage, and standard deviations were computed to summarize the categorical variables. The analysis was done using R programming software. Association between the outcome and the independent variables was taken as statistically significant at $P < 0.05$.

### Inclusion criteria

All patients with suspected first-line ART failure (either clinical and/or immunological from respective ART Center) within 5 years of first-line ART initiation referred to the Centre of Excellence and attended SACEP meeting of STM for virologic confirmation were included as study participants.

### Exclusion criteria

The exclusion criteria were

1. Pregnancy
2. Children <18 years.

## Operational definitions

Treatment failure on first-line ART can be categorized as virological failure, immunological failure, clinical failure, or some combination of three.

1. Virological failure: Viral failure is defined by a persistently detectable VL exceeding 1000 copies/ml (that is, two consecutive VL measurements within a 3-month interval, with adherence support between measurements) after at least 6 months of starting a new ART regimen
2. Immunological failure: It is defined as a suboptimal immunologic response to therapy or an immunologic decline while on therapy. Decrease in CD4 cell count to pretherapy baseline level (or below); 50% decrease from the peak value during treatment; and persistent low CD4 cell counts of <100 cells/mm$^3$ after at least 12 months of ART
3. Clinical failure: Occurrence of a new WHO stage III or IV opportunistic diseases while on treatment. It represents the most urgent and concerning type of treatment failure and should prompt an immediate evaluation.[9,10]

Adherence involves a mutual decision-making process between client/patient and health-care provider. Pill count is the most commonly used method to assess the adherence.

Following formula was used to calculate adherence.

Adherence (%)=100× (Total number of pills the patient has actually taken/Total number of pills should have been taken in that time period by the patient). Suboptimal adherence is defined <95% of adherence.

First-line ART regimen constitutes by the combination of two NRTI and one NNRTI. Second-line ART was defined as the regimen used for the treatment of patients living with HIV who failed the first-line regimen, and typically, it would consist of a PI (e.g., atazanavir/lopinavir boosted with ritonavir) and two or three NRTIs (e.g., lamivudine and tenofovir ± zidovudine).

## RESULTS

A total of 190 patients were referred to SACEP for evaluation, treatment failure was assessed based on the NACO criteria, and in this study, 100 (52.6%) patients, i.e., 78 (41.06%) males and 22 (11.57) females had failed the first-line regimen (plasma VL ≥1000 copies/ml) and need to switch to the second-line drugs. The median age was 37 years (range 8–65 years) and the median duration of the first-line ART taken was 2.85 years, range 0.05–10.08 years. In this cohort, the mean duration to detect treatment failure indicates the time between ART initiation and the detection of failure of the first-line ART at the time of referral. Different combination ART regimens were compared, and accordingly, zidovudine, lamivudine, and nevirapine (ZLN) combination therapy was the most common (45 patients) regimen followed by stavudine, lamivudine, and nevirapine (21 patients); zidovudine, lamivudine, and efavirenz (17 patients); tenofovir, lamivudine, and nevirapine (8 patients); and tenofovir, lamivudine, and efavirenz (6 patients); and stavudine, lamivudine, and efavirenz (3 patients). The study revealed that the majority of the patients, i.e., 77 (40.5%) were asymptomatic (stage 1); only 15 (7.9%) and 23 (12.1%) patients were in very advanced stage (WHO stage 3 and 4) at the time of SACEP referral. In 59 (31%) patients, CD4 count fell below baseline value; in 50 (26.3%) patients, CD4 dropped ≥50% of their peak value; and in 48 (25.3%) patients, it was persistently low, i.e., <100 cells/cmm at the time of referral. Among 100 patients who failed the first-line ARVs, 73 (38.4%) patients were referred only for immunological failure, 26 (13.7%) patients for both immunological and clinical failure, and only single (0.52%) patient for clinical failure.

Adherence to ART was assessed, and the study showed that 55 (28.94%) patients with suboptimal adherence and 45 patients with optimal adherence to first-line drugs had VL ≥1000 copies/ml [Table 1].

## DISCUSSION

First-line ARV treatment failure is a growing problem in India, and remaining on a failing regimen increases the chance of development of drug resistance which simultaneously complicates the construction of new potent second-line regimen and increases mortality in HIV-infected patients.[11,12] Hence, it is very important to identify the first-line treatment failure patients very early and to switch them to second-line ARV.

We found that male patients (41.06%) outnumbered the female (11.57%) failing first-line ART. Rajasekaran *et al*. also reported similar finding in their study.[13]

This study shows that the median duration of first-line ART taken was 2.85 years, range 0.05–10.08 years. Abiyie Zeleke concluded that prolong first line ART intake (>60 months) along with ARV prophylaxis

**Table 1: Characterization of patients who failed first-line antiretroviral therapy**

| Variable | PVL <1000 copies/ml, no of patients (%) | PVL ≥1000 copies/ml, no of patients (%) | No of patients (%) |
|---|---|---|---|
| Total patient | 90 (47.4) | 100 (52.6) | 190 (100) |
| Male | 66 (34.74) | 78 (41.06) | 144 (75.8) |
| Female | 24 (12.63) | 22 (11.57) | 46 (24.2) |
| Regimen | | | |
| SLE | 5 (2.63) | 3 (1.57) | 8 (4.2) |
| SLN | 15 (7.89) | 21 (11.01) | 36 (18.9) |
| TLE | 1 (0.54) | 6 (3.16) | 7 (3.7) |
| TLN | 7 (3.69) | 8 (4.21) | 15 (7.9) |
| ZLE | 9 (4.76) | 17 (8.94) | 26 (13.7) |
| ZLN | 53 (28) | 45 (23.6) | 98 (51.6) |
| WHO T-stage at the time of referral | | | |
| Stage 1 | 68 (35.8) | 77 (40.5) | 145 (76.3) |
| Stage2 | 3 (1.55) | 6 (3.15) | 9 (4.7) |
| Stage 3 | 13 (6.8) | 15 (7.9) | 28 (14.7) |
| Stage 4 | 15 (7.9) | 23 (12.1) | 38 (20) |
| CD4 count at the time of referral | | | |
| 1. CD4 <baseline | 52 (27.4) | 59 (31) | 111 (58.4) |
| 2. >50% drop from peak value | 37 (19.5) | 50 (26.3) | 87 (45.8) |
| 3. Persistently ≤100/ml | 27 (14.2) | 48 (25.3) | 75 (39.5) |
| Reason of SACEP referral | | | |
| Clinical | 3 (1.58) | 1 (0.52) | 4 (2.1) |
| Immunological | 69 (36.3) | 73 (38.4) | 142 (74.7) |
| Both | 18 (9.5) | 26 (13.7) | 44 (23.2) |
| Adherence | | | |
| Good | 76 (40) | 45 (23.7) | 121 (63.7) |
| Poor | 14 (7.37) | 55 (28.93) | 69 (36.3) |

PVL=Plasma viral load; SACEP=State AIDS Clinical Expert Panel; SLE=Stavudine-Lamivudine-Efavirenz; SLN=Stavudine-Lamivudine-Nevirapine; TLE=Tenofovir-Lamivudine-Efavirenz; TLN=Tenofovir- Lamivudine- Nevirapine; ZLE=Zidovudine- Lamivudine-Efavirenz; ZLN=Zidovudine- Lamivudine-Nevirapine

for PMTCT, advanced clinical stages (3 and 4), low base line CD4 value (<200 cells/μl), tuberculosis co-infection, substitution of regimen once or more for any reason, poor adherence were independent risk factors for ART treatment failure.[14]

In this study, we found that 45 (23.6%) patients took ZLN, followed by SLN and TLN as first-line ARV; TLE was taken by least number of patients. Babo *et al*. reported in their study that stavudine, lamivudine, and nevirapine combination were the most common drugs taken by the failure patients.[15] There is a growing body of evidence from observational studies that in routine settings, the use of NVP is associated with a greater risk of virologic failure. Data in their study have yielded that people on nevirapine-based ARV failed more than efavirenz-based regimen.[16] As we took data of patients of 2013 and 2015 and NACO recommended TLE as the first-line drug since December 2014, we did not have a large number of patients on TLE as line drugs.

Ayalew *et al*. in 2016 reported that poor adherence to treatment and low CD4 count were the two most important associations responsible for first-line treatment failure.[16]

We found that drug nonadherence has the strongest correlation with treatment failure in our study participants. There was a significant association between poor adherence and treatment failure ($P < 0.05$). [Table 2] Babo *et al*. also revealed that ART treatment interruption was an important factor for the first-line treatment.[15] However, contrary to other study, we found no significant association between low baseline CD4 count and treatment failure.[16] [Table 3] Khienprasit *et al*. also published that lower baseline CD4 cell count was one of the main factors significantly associated with ART failure.[17]

One of the strengths of this study is the relatively large sample size with individual patient follow-up time data. The study was also conducted within the routine program setting which reflects ground reality.

Various studies have shown that advanced disease stage was a significant predictor of treatment

failure explained by the frequent occurrence of opportunistic infections.[18,19]

One important finding in this study is that among the first line ART failure patients, 1 (0.52%) patients presented with clinical failure, 73 (38.42%) patients with immunological failure and 26 (13.7%) patients with both clinical and immunological failure. No significant association was noted with aforesaid presentation and plasma viral load. [Table 4] Studies in East Africa have shown a high prevalence of immunologic failure ranging from 8% to 57% among clients on first-line HAART, and furthermore, the magnitude increases as the time of follow-up increases.[19,20]

Although VL monitoring is the gold standard method to diagnose ART failure, it is not possible for all PLHIV in resource-limited setting like India. Diagnosis and monitoring of first-line treatment failure and the decision to initiate second-line treatment are largely based on the clinical and immunologic assessment of patients. This study yielded a valuable insight to the various characteristics of treatment failure.

**Table 2: Poor adherence and viral load are independent**

| Adherence | Viral load | |
|---|---|---|
| | Failure (≥1000 copies/ml) | NonFailure (<1000 copies/ml) |
| Optimal | 45 | 76 |
| Suboptimal | 55 | 14 |

Pearson's Chi-squared test with Yates' continuity correction $\chi^2$=30.1837, df=1, *P*=3.93e-08 (<0.05). As *P*<0.05, we conclude that viral load and poor adherence are not independent, i.e., there is an association between poor adherence and viral load

**Table 3: Baseline CD4 value <100cells/ml and viral load are independent**

| Baseline CD4 <100/cmm | Viral load | |
|---|---|---|
| | Failure (≥1000 copies/ml) | Non Failure (<1000 copies/ml) |
| No | 51 | 52 |
| Yes | 49 | 38 |

Pearson's Chi-squared test with Yates' continuity correction. $\chi^2$=0.6248, df=1, *P*=0.4293 (>0.05). The *P*>0.05. We accept the null hypothesis that baseline CD4 <100 and viral load are independent

**Table 4: Criteria for referral and viral load are independent**

| Criteria for referral | Viral load | |
|---|---|---|
| | Failure (≥1000 copies/ml) | Non Failure (<1000 copies/ml) |
| Clinical | 1 (0.52%) | 3 (1.58%) |
| Immunological | 73 (38.4%) | 69 (36.3%) |
| Both clinical and immunological | 26 (13.7%) | 18 (9.5%) |

Pearson's Chi-squared test with Yates' continuity correction. $\chi^2$=2.0466, df=1, *P*=0.3594. *P* value for the test >0.05. We accept the null hypothesis, and there is no association between the referral criteria and viral load

## CONCLUSION

In the present retrospective cohort study, we observed that decreased adherence to anti-retroviral treatment is the most important factor responsible for early first-line treatment failure. Our findings suggest that as adherence is a dynamic process, interventions in every visit following ART initiation should be optimized and a multidisciplinary approach toward adherence is needed to get the highest treatment outcome benefit.

### Acknowledgment

We are very much thankful to our patients for their cooperation and all the staffs of Centre of Excellence who helped us in this study.

We are thankful to Mrs. Snigdha Pain for helping us with statistical analysis.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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