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Research Article

Prevalence of Failure of First-Line Anti-Retroviral Therapy in HIV Patients: A Retrospective Cross-Sectional Study of Six Districts of Andhra Pradesh Over One Decade

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Abstract: National ART program was launched on 1st April 2004. As the treatment is life long, failure rates need to be assessed periodically, to assess the efficacy of first-line ART (Anti-Retroviral Therapy). This is the largest retrospective, cross-sectional study, from April 2004 to March 2014, conducted at ART–Plus Center, in Government Siddhartha Medical College and Government General Hospital, a tertiary level teaching hospital at Vijayawada, Andhra Pradesh, India. The study population was PLWHA (people living with HIV & AIDS), registered for first-line ART, in 16 nodal ART centers, from 6 districts of Andhra Pradesh (before state bifurcation). We calculated failure of first-line ART and we also analyzed the significance of duration of ART, gender, and base line CD4 count on the prevalence of first-line ART failure. Out of total 57,674 subjects who were on first-line ART, 244 subjects needed second-line ART, with prevalence of first-line ART failure as 0.47%. Mean duration of therapy was 53±23.44 months. There was no significant association between mean duration of ART and first-line ART failure. Males (189) had significantly higher failure rate compared to females (55); (χ^2 =84.03; p = <0.05). There was significant association between low CD4 count and failure of first-line ART (χ^2 =15.48; p = <0.05). Our study has shown that first-line ART in the National ART program is still effective. Second-line ART may be needed only in areas with high prevalence of first-line ART failure.
Keywords: Anti-Retroviral Therapy, CD4 count, Drug resistance, First-line Art, Resource limited settings, Treatment failure.

INTRODUCTION

Government of India launched the free National ART program on 1st April 2004. As on March 2013, there are around 18.13 lakhs people living with HIV (PLHIV) in India. Currently near 6.5 lakhs are on first-line ART. India is estimated to have around 1.16 lakhs annual new HIV infections among adults. The six high prevalence states account for only 31% of new infections, while the ten low prevalence states of Odisha, Jharkand, Bihar, Uttar Pradesh, West Bengal, Gujarat, Chattisgarh, Rajasthan, Punjab & Uttarakhand together account for 57% of new infections. The four high prevalence states in South India (Andhra Pradesh, Karnataka, Maharashtra and Tamilnadu) account for 53% of all HIV infected population in the country [1].

The introduction of HAART (Highly Active Anti-Retroviral Therapy) has led to an increase in survival among HIV-infected patients, decreased HIV-associated mortality, and improved quality of life among HIV patients. In India, under the National Aids control program (NACO), the generic fixed drug combination of zidovudine (or) Stavudine, Lamivudine and nevirapine (or) efavirenz is being used. Despite the reduction in morbidity and mortality, a considerable proportion of patients fail to achieve a sustained virological response to therapy [2].

In the resource limited setting like India, where the cost of treatment is very high and where routine virological monitoring and genotyping resistance is not done to start the therapy and see the response to therapy, there is a need for parameters to stratify the patient in to different stages of risk of failure, which will be useful for the clinicians. In routine clinical practice, where monitoring of ART adherence, investigations to assess the failure, and clinical follow-up are generally less rigorous, failure rates are often higher [2].

India has the second largest burden in the world after South Africa. There are few data on the incidence and risk factors for treatment failure associated with generic HAART regimens in India. Treatment failure is an increasing concern [3].

Since 2004 with extension of ART program to all over India, increased number of HIV patients have got access to treatment. With increased duration of treatment years as well as quantum of patients, we expect some failure rates to first-line ART. Failure rates to first-line ART may vary region wise and need not be uniform all over the country due to various identified reasons.

To our knowledge, ours is the largest retrospective cross-sectional study in India on the prevalence of failure of first-line ART, over one decade, covering six districts of combined Andhra Pradesh. Our objectives were a) to study the prevalence of failure of first-line ART and b) to study the statistical significance of association of first-line ART failure with duration of ART, gender, and base line CD4 count.

MATERIALS AND METHODS

Our study was a retrospective cross-sectional study from April 2004 – March 2014, a period of 10years. This study was done at ART-Plus centre, established in Government Siddhartha Medical College and Government General Hospital, a tertiary level teaching hospital at Vijayawada, Andhra Pradesh, India. This study was approved by institutional ethics committee. This ART-Plus centre is a referral centre and serves six districts, namely Krishna, Guntur, West Godavari, Nellore, Prakasam and Khammam districts of Andhra Pradesh (before state bifurcation), in relation to confirmation of first-line ART failure and provision of second-line ART (Fig.1). This centre follows national guidelines for treatment of HIV patients.

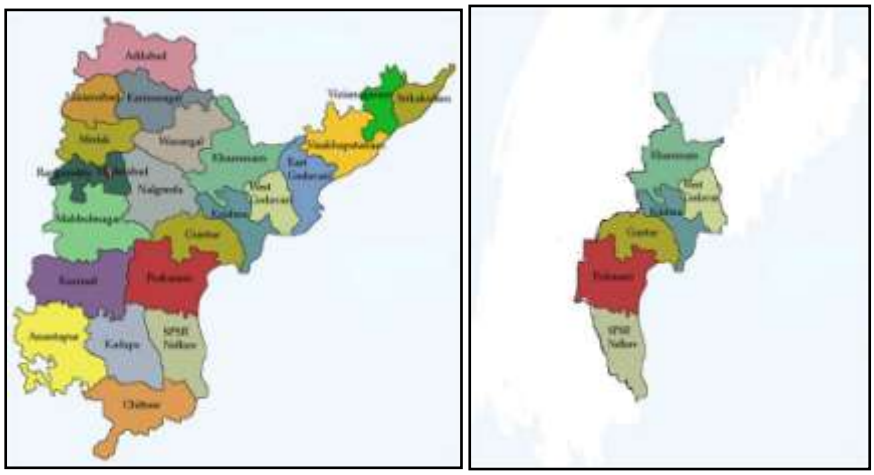

Fig. 1: Districts covered in our study

Study population included PLWHA, registered for first-line ART in the 16 nodal ART centres, from 6 districts. Study duration was a decade spanning from April 2004-March 2014. Among study population males were 27,797 and females were 29,877.

Inclusion criteria

- Subjects of > 15 years of age, on first-line ART
- Subjects on first-line ART, with at least one follow-up visit at 6 months
- Patients switched over to second-line as per NACO guidelines.

Exclusion criteria

- Children of <15 years age, who are on ART
- Pregnant and lactating women
- Subjects on alternate first-line ART

We calculated the prevalence of failure of first-line ART. We also assessed the statistical significance of association of first-line ART failure with a) duration of ART, b) gender and c) base line CD4 count. The data was collected retrospectively from the electronic health record (EHR) of the ART-Plus centre, Vijayawada. The EHR contains complete information of each patient, including demographics, HIV risk behaviors, adherence to ART, medications, which are entered as a part of routine clinical documentation and which is updated every day. Patients, whose complete record was not available and patients who could not be traced, were excluded from the study.

Treatment Failure

Treatment failure was assessed using definitions of ART failure given by WHO [4]. Clinical failure was defined as new or recurrent WHO stage4 condition, after at least 6 months of ART. Immunological failure was defined as fall of CD4 counts to pre-therapy baseline or below; 50% fall from the on-treatment peak value; and persistent CD4 levels below 100 cells/mm^3. Virological failure was defined as plasma viral load >5,000 copies /ml, after at least 6 months of Art.

Statistical analysis

The data was analysed by using MS excel. The data were presented by mean ± standard deviation for continuous variables. Chi-square test and *P* values were used to assess the statistical significance of the findings.

P value <0.05 were considered as statistically significant.

Table 1: Baseline characteristics of patients

Variable	Value
Males	27,797
Females	29,877
Mean baseline CD4 count ± SD (months)	191.63±181.86
Mean duration of ART±SD (months)	53±23.44

RESULTS

Out of total 57,674 individuals, 244 had failure, with prevalence of failure of first-line ART 0.47%. There was no significant association of duration of ART with first-line ART failure with χ^2 =0.0069; *P* >0.05 (Table 2).

Males had higher incidence of first-line ART failure than females with statistically significant values, χ^2 =84.03 and *p*<0.05 (Table 3).

First-line ART failure was found in 180 subjects with less than mean CD4 count and in 64 subjects with more than mean CD4 count. There was significant association between low mean CD4 count and first-line ART failure with χ^2 =15.48 and *p*=<0.05 (Table 4).

Table 2: Duration of ART vs First-line ART failure

Mean duration (Months) (53±23.44)	First-line failure (n)	First-line effective (n)	Total (n)
<Mean	145	34,280	34,425
>Mean	99	23,150	23,249
Total	244	57,430	57,674

Table 3: Gender vs First - line ART failure

Gender	First-line failure (n)	First-line Effective (n)	Total (n)
Males	189	27,608	27,797
Females	55	29,822	29,877
Total	244	57,430	57,674

Table 4: Mean Baseline CD4 vs First-line ART failure

Mean (191.63±181.86)	First-line failure (n)	First-line Effective (n)	Total (n)
<Mean	180	35,314	35,494
>Mean	64	22,116	22,180
Total	244	57,430	57,674

Table 5: Frequency of types of failures in our study

Virological failure	222 (90.1%)
Immunological failure	188 (77%)
Clinical failure	23 (9.4%)
Both clinical & immunological	37 (15.2%)

DISCUSSION

To our knowledge ours is the ever largest study on the prevalence of failure of first-line ART, conducted in combined Andhra Pradesh (before bifurcation). Major problem of long-run programs is treatment failure. Prevalence of treatment failure need not be uniform all over country. Prevalence of treatment failures may be heterogeneous and may vary from region to region or states. So it is desired to estimate prevalence of treatment failure at frequent intervals, so that second-line drugs can be introduced only in regions with high prevalence of first-line ART failure.

India has the second greatest HIV burden in the world after South Africa. Monitoring the efficacy of treatment in countries with limited resources is difficult. Unnecessary switching to second -line ART drugs may be a burden is countries like India, with financial constraints. So continuation of first-line ART is cost effective in resource limited settings, especially in

places where prevalence of first-line ART failure is low. Accordingly specific group of patients who meet the NACO definitions of failure criteria, may be switched over to second-line ART.

Some of the studies published their findings about first-line ART failure. In a study from South India in 2004, 40 of 1,443 patients (14%) experienced treatment failure at a mean of 406 days [5]. Dragsted *et al*. have reported that the incidence of treatment failure at 12 months was 11.6 per 100 person-years of follow-up, and that reduced over time [6]. Rajasekaran *et al*. reported in their study that cumulative incidence of treatment failure among 1370 patients was 3.9% [3]. Treat Asia HIV observational database (TAHOD) showed that the rate of clinical failure was 7.3 per 100 people-years [7]. Our study was the largest study, covering a period of a decade, including 57,674 subjects. Our study documented that prevalence of failure of first-line ART was only 0.47%, indicating the efficacy of first-line ART.

There were reports about predictors of failure of first-line and ART. Rajasekaran *et al*. reported that negative change in absolute lymphocyte count, hemoglobin concentrations and body weight during follow-up as inexpensive predictors of failure of first-line ART [3]. Male patients had a 3.5 times significantly greater hazard ratio for treatment failure compared with female patients [3]. Patients from urban areas had 1.9 times greater hazard ratio compared to rural areas [3, 5], which may reflect possible involvement in high-risk behavior.

Anup Singh *et al*. reported that low baseline CD4 count, lower peak CD4 count achieved, early and lower level of plateau of CD4 count were as important predictors of first-line ART failure [2]. They also documented that co-infection with tuberculosis, older age, and male sex were important predictors of first-line ART failure. Laurence Ahoua et al, found that older age group of patients of >35 years of age were more likely to fail with first-line ART [8]. Deeks *et al*. have shown that base line CD4 count was associated with treatment failure [9]. These predictors can be used for close follow-up to identify the treatment failure early and assist policy makers in planning second-line treatment regimens where required. Some of the recent cohort studies and RCTs suggested that baseline and time-updated CD4 cell counts are better predictors of HIV-1 disease progression than are Plasma Viral Loads (PVLs) [10, 11]. A lower risk of clinical progression was reported among female patients with intermediate baseline viral load than in males [12].

Adherence is important in achieving suppression with an ART regimen. Adherence begins to wane after the first month of therapy. So, closer assessment of adherence particularly after first month of therapy is important [13]. Suboptimal adherence to these regimens has been postulated to be one of the main factors associated with decreased HIV suppression as well as for the emergence of resistant virus [14, 15].

Prevalence of primary HIV drug resistance mutations (DRMs) in northern India is 2.9% and <5% in Kakinada of southern India, which are within the threshold limit of <5% [16, 17]. This finding reinforces the National ART program's effort in maintaining low level of primary ART drug resistance. Until the baseline HIV genotyping becomes more affordable, there is a need for Periodical studies to assess primary ART drug resistance from different regions of India.

Kumaraswamy *et al*. reported that 20% of patients modified their first-line ART regimen and the most common reason for modifying therapy was development of adverse reactions and treatment failure was less common cause [5, 18].

The association between HIV infection and tuberculosis is complex and bi-directional [19]. The effect of tuberculosis on HIV replication is mediated by cytokines IL-1, IL-6, and TNFα, which in turn results in enhanced viral replication [20].

TAHOD study has shown that treatment with the simple fixed-dose combination Stavudine, Lamivudine, and Nevirapine was safe and effective, with good adherence and tolerability and also adverse events are the common reason for treatment change [7, 21].

CONCLUSION

- Prevalence of failure of first-line ART was 0.47%.
- No significant association between mean duration and failure of first-line ART.
- Males had higher incidence of first-line ART failure, compared to females.
- Low mean CD4 counts were associated with higher failure rates.

Low prevalence of failure in our study indicates that first-line ART is still effective and can be continued, especially in resource limited settings like India. But as duration of therapy is longer of many years, there is a chance for development of resistance. As a result, prevalence of first-line ART failure need to be assessed periodically in different parts of the country, so that second-line ART may be needed only in regions with high failure rates. Routine virological monitoring and genotyping resistance is not practicable at present in our country. So it is ideal to monitor ART with watchfulness and using non-expensive criteria like thorough clinical history, adherence to treatment, hemoglobin level, total lymphocyte count, body weight measurement, peak CD4 count, and treatment of opportunistic infections [22]. Good adherence also reduces incidence of drug resistance. This is the ideal procedure until routine virological monitoring and

testing for primary drug resistance becomes affordable in our country.

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