

# Role of different HAART regimens in ART program of INDIA on Missing appointments of On Treatment PLHIVs in Srikakulam.

Dr. K. Sunil Naik\*, Dr. Kiran Anaparthi\*\*, Dr. Yadlapalli Ratna Sree\*\*\*

\*Assistant professor, Department of General Medicine, Rajiv Institute of Medical Sciences, Srikakulam.

\* In-charge Medical officer, Anti-Retroviral Treatment Centre (ARTC), Rajiv Institute of Medical Sciences, Srikakulam.

\*\* Medical officer, Anti-Retroviral Treatment Centre (ARTC), Rajiv Institute of Medical Sciences, Srikakulam.

**Abstract-** Missing regular appointments to ART centres in Srikakulam have increased by over 5% in the last one years. In 2015, between January to June, with the help of staff of ARTC, RIMS GH, Srikakulam, we conducted a retrospective cohort study in srikakulam district of Andhra Pradesh. PLHIV of age group 15-74, and regular on treatment at srikakulam by the end of DEC 2014 were considered for study at 50:50 gender ratio. In the study, a total of 1258 new missed appointments were found out of 22800 scheduled appointments. The most frequently reported drug regimen in missed appointments were TDF+3TC+EFV (TLE) (752 episodes), ZDV+3TC+NVP (ZLN) (442 episodes) and ZDV+3TC+EFV (ZLE) (56 episodes), and 24-44 age group has a share of 70% new miss. So, we recommend a thorough relook into national guidelines for implementation of TLE as single drug, owing to its high rate of missing appointments in productive age group (25-44 years) as it may hamper the national program and a further study recommended for cause of rejection of regimen in PLHIV is much needed.

**Index Terms-** Tenofovir (TDF), Effavirin (EFV), Adherence, Resistance, missing HAART.

## I. INTRODUCTION

At the end of March 2015, an estimated 36.9 million people were living with the human immunodeficiency virus (HIV) worldwide and 15 million were receiving life-saving antiretroviral treatment (ART) worldwide [1]. Despite scaling up ART in low- and middle-income countries, an estimated 41% coverage of those in need of ART have access to ARV drugs. Universal access to treatment (defined as 80% or greater coverage) is thus still to be achieved in almost all parts of the world [1].

In India, the total number of people living with HIV/AIDS (PLHIV) was estimated at 2,100,000 in 2012 [2]. In recent years, the country has put considerable efforts in expanding HIV-testing sites, and about 200,000 new HIV-positive individuals are diagnosed each year [2]. Access to CD4-testing facilities and ART centres has also been expanded. Despite establishment of Link ART centres and Link ART plus centres in ICTCs with concept to reduce time, cost, of travel to ARTC and to increase adherence to ARV drugs through national program, late presentation of patients to ART sites who are

receiving ARV drugs is known to be an operational challenge for two major reasons. One is failure to reach to LAC and LAC+ centres owing to stigma for the near place and; and the other is failure to attend ARTC for timely refill of ARV drugs owing to longer distance.

In the State of Andhra Pradesh in south India, HIV-testing sites and ART facilities have been scaled up dramatically to increase access to testing and treatment from Nation program. However, HIV-testing sites are physically disconnected from ART centres. While HIV-testing facilities are available at the primary healthcare level, ART centres are situated mostly at the district level. For an HIV-reactive individual (sick or healthy), this thus implies a ‘‘journey’’ from diagnosis to care that involves travel, time and other direct and indirect costs. In Srikakulam, in spite of having 12200 registered cases [3], we are having only one ART centre to cover total district that made PLHIV to travel more than 100km to reach ARTC and another 100 km to reach their homes.

In the Srikakulam District of AP, we thus determined to have a look at the role of ART regimens used as per revised national guidelines for any possible impact for missing the scheduled appointments to ARTC as, it has been shown that virological suppression can be achieved if high level of adherence was maintained [4].

## II. STUDY DESIGN

This was a Retrospective Cohort study involving a review of records routinely maintained under the National AIDS Control Programme (NACP).

### Study setting, sites and study population:-

Srikakulam district with a population of 2.71 million, is one of the smallest district in state of Andhra Pradesh of India and is considered to have a relatively advanced HIV epidemic [5]. In 2009, the district had an HIV prevalence of <0.50% [6]. There are 17 public HIV-testing sites (16 are standalone, while 1 mobile testing centre) and 1 ART centre with 3 Link ARTC+ and 6 LACs. All HIV-positive persons diagnosed at the HIV testing sites are referred to the nearest ART centre for further management and are expected to reach these ART centres on their own. ART centre, located at tertiary care medical college of the district, Rajiv Gandhi Institute of medical sciences, far from the point of HIV diagnosis; distances are in the range of 5-120 km, and they are often not well connected by public transport.

TABLE 1

Status	Total(n)	n (%)
D	118	0.52
LFU	177	0.78
MIS	1579	6.93
OT	20822	91.32
ST	4	0.02
ST-P	8	0.04
T	92	0.40
<b>TOTAL</b>	<b>22800</b>	<b>100.00</b>

Patients most often have to spend a whole day for each visit to the ART centre.

On arrival at ART centres, patients are registered, given a pre-ART registration number and classified into World Health Organization (WHO) clinical stages. They then undergo basic investigations, including CD4 count assessments, and if found ART eligible they are initiated on ART and followed up monthly. Those who are not eligible for ART are asked to return for six monthly follow-ups, including a CD4 assessment.

ART eligibility assessments were done in accordance with national guidelines, which are in tune with current WHO recommendations [7]. Briefly, any person in WHO clinical stages 1 or 2 with a CD4 count  $\leq 350$  cells/mm<sup>3</sup> and anyone in stages 3 or 4 irrespective of CD4 count were eligible for ART, pregnant women, and patients with TB are started on HAART. Srikakulam district has District AIDS Prevention and Control Units (DAPCUs) monitoring the operations under NACP. Each unit is headed by a district-level Programme officer who in turn is assisted by paramedical staffs to monitor the process of linking HIV-positive persons who were diagnosed at HIV testing sites to the ART centres, and to maintain information on all of the HIV-positive patients detected in their respective districts.

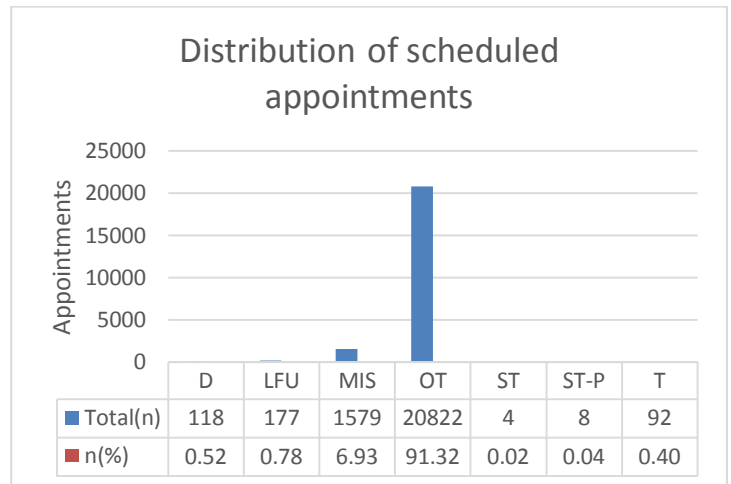
This study was conducted at ARTC, RIMS, Srikakulam from January 2015 to June 2015, across the district on PLHIV who are alive and on treatment and are scheduled to pick up medicines in January 2015.

**Data and statistical analysis:-**

The sources of data were HIV-testing records and ART centre records (pre-ART registers, ART enrolment registers and patient treatment cards). For each patient, we reviewed the records through the end of June 2015 from January 2015 to ascertain whether the respective patient had complete updated record. The data was cross checked with Dec 2015 visit and due dates. A total of 3800 PLHIV who took medicine in Dec 2014 and scheduled for Jan 2015 were sampled for next 6 months follow up. A total of 22800 scheduled visits for these 3800 PLHIV for next 6 months were considered in this study and followed up. The data analysis and RR, 95% CI, P-value are calculated using Medcalc software.

III. RESULTS

A total of 3800 PLHIV with total scheduled visits of 22800(n) at 50:50 gender ration, 1900 are male and 1900 are female with each having scheduled appointments of 11400 each and the mean (SD) age was 35 years.



Of those scheduled visits for refill of HAART(Table 1), 20822 (91.32%) visits were as per schedule and picked up their respective pill box, 118 (0.52%) visits were marked as Death, 177 (0.78%) visits were marked as Lost to Follow up (LFU), 1579 (6.93%) were marked as total missed appointments, 12 (0.05%) were marked as stopped owing to health problems, and 92(0.40%) were marked as transferred out to other centres.

Overall missed appointments were 1579 standing at 6.93% of total appointments of which 1258 were marked as new miss and other 321 visits were repeat miss following last month miss appointment. Of 1258 new misses that were considered for study (Table 2), 636 (50.55%) were scheduled for males and 622 (49.44%) were scheduled for female. Of 1258 new misses, 445 (35.37%) were 25-34 years age group and 461 (36.65%) were 35-44 age group causing 70.02% of total new miss. And again, of 1258 miss recorded, 752(59.78%) were recorded among PLHIV using TDF+3TC+EFV (TLE) regimen and 442(35.14%) among PLHIV using ZDV+3TC+NVP and found that TLE regimen got RR of 1.63 (CI 1.14 - 1081 and p value <0.0001).

IV. DISCUSSION

This is one of the studies in India that assessed the cause of regimens for the linkage between regular HAART usage and Missing of appointments at ART centres, and it shows that about 60% of PLHIV who were recorded as new miss were due to use of TDF+3TC+EFV regimen and two thirds of miss were caused by EFV based regimen when compared to NVP based regimen.

A key finding of this study is that, in the ‘‘linkage pathway’’ between HAART prescription and missing of appointments, 91.32% of HIV-positive individuals were retained in care as per schedule and 6.93% of those who were on treatment were missed over the period of 6 months. A recent study estimated a relatively high rate of patients in VF while among them an important proportion harbored wild-type viruses and this highlights a real need to reinforce treatment adherence [8]. Since missing new cases to TLE, may be a point of view to enhance chance to increase adherence by some corrections in the national program.

Firstly, since over 26% of attrition was related to early deaths at the stages of HIV testing and ART eligibility, it is likely to reflect late presentation of patients and advanced disease. A recent study from India showed that 85% of patients

present late to health facilities [9]. Accordingly, late presentation to ARTC after HIV testing along with regular missing of scheduled pick up of refill will culminate proportionately to increase wild type virus [8], causing illness and death, and we lost total scheduled appointments 0.52% to deaths in our study.

Second, to the point of concern, the high proportion of new miss (70.02%) were within age group between 25-44, which is considered to be earning age group and is backbone to Indian economy in future, are also missing at higher number even with better care and decentralized service for care of PLHIV and there is a clear need to decentralize ART further and bridge the geographical disconnect between HIV testing and care, as separate (disconnected) services are known to result in lower ART uptake [9].

Third, as a process of implementation of TLE as a single best regimen for all [7], i.e., treating PLHIV, PEP, ANC cases infected with HIV, by WHO and NACO in India, we tend to study nature of new miss to analyze chances of different regimens as a cause of new miss. Further into the study, we selected the scheduled appointments in spite of number of PLHIV on treatment, to fast identify each appointment effectively and to reduce errors caused by repeat misses by the PLHIV. In the process, we described MIS as the failure of PLHIV to pick the medicine at ARTC in the scheduled month and the first missed appointment is calculated and if the PLHIV is missed for 3 months, then it is labelled as 'LFU' [10]. Again, if a PLHIV picked medicine in January and dint turn up in Feb but again visited in March for the refill and was miss again in April, i.e., alternate month MIS, then the both missed appointments are calculated as new miss, as each missed month was preceded by visit having a counselling session at ARTC, consisting of importance of HARRT and resistance to the drugs, and clarification on side effects of the regimen.

Of all the new missed appointments occurred during the study period, regimens TLE (RR 1.63, CI 1.14 - 1081) with significant P-value of <0.0001 and ZLN (RR 0.63, CI 0.55 - 0.70) with p-value <0.0001. These two regimens has caused a significant number of new miss and again, TLE has relatively increased risk (1.63 times) of missing an appointment than other regimens in the national guidelines in India. In this context, a point to compare, even ZLE (RR 1.06, CI 0.81 - 1.37) with p-value of 0.55 has a considerably higher risk of missing the appointment.

A very encouraging finding from the study [11] is that almost all (i.e. all but one) co-infected HIV-TB patient and all HIV-positive pregnant women reached ART centres which is very encouraging as compared to results of studies elsewhere [12,13]. As per the study provided [11], the initiation of HAART in ANC infected with HIV and TB co-infected patients in India is absolutely 100 %, and these are group of persons needed to be started on TLE [7, 10] or else ZLE, in cases of known toxicities for TDF based regimen, culminating the risk of missing new cases with the prescribed regimen is at its higher level which may disrupt the RNTCP and PPTCT programs in India. This merits further investigation into using the regimen.

The strengths of this study are that patients were rigorously counselled on drug use ranging from 6 months to more than 4 years, as the group selected for the study has a HAART initiation date as long as 12/05/2007 and latest date as

31/7/2015. We tried to explore reasons for miss through telephone calls and outreach visits and, the data come from routine clinics as it is likely to reflect the on-the-ground reality. We also adhered to the guidelines for reporting of observational studies [14] and ethics [15]. Limitations include the fact that roughly 1.75% of patients who were lost to follow-up, died and transferred out.

## V. CONCLUSION

In Srikakulam, a small district of Andhra Pradesh, state of India, 59.78% of all new missed appointments of scheduled appointments were lost due to TLE regimen and another 35.14% lost to ZLN but in numbers, a massive difference of 310 new missed recorded towards a future regimen in productive age group of 24-44 years (causing 70% new miss), which is of considerable problem in respect of using it towards the single regimen in the ground level and requires to re think in national guidelines.

## REFERENCES

1. UNAIDS. Fact sheet global statistics-2014. How AIDS changed everything?
2. UNAIDS global report 2013 and NACO HIV estimates 2012.
3. Monthly report submitted to NACO by ARTC.
4. Jiamsakul A et al. Journal of the International AIDS Society 2014, 17:19053, HIV multi-drug resistance at first-line antiretroviral failure and subsequent virological response in Asia
5. Census of INDIA 2011.
6. HIV/AIDS Situation and Response in Srikakulam District: Epidemiological Appraisal Using Data Triangulation
7. 2013 WHO guidelines for HAART initiation and follow up.
8. Antiretroviral treatment outcome in HIV-1-infected patients routinely followed up in capital cities and remote areas of Senegal, Mali and Guinea-Conakry. Diouara AAM et al. Journal of the International AIDS Society 2014, 17:19315.
9. Sogarwal R, Bachani D. Are persons living with HIV timely accessing ART services in India? J Indian Med Assoc. 2009;107(5):288\_90, 307.
10. Revised NACO guideline for ARTC 2014.
11. Shastri S et al. Journal of the International AIDS Society 2013, 16:18502
12. Harries AD, Lawn SD, Getahun H, Zachariah R, Havlir DV. HIV and tuberculosis \_ science and implementation to turn the tide and reduce deaths. J Int AIDS Soc. 2012;15(2):17396. doi: 10.7448/IAS.15.2.17396.
13. Zachariah R, Teck R, Ascurra O, Gomani P, Manzi M, Humblet P, et al. Can we get more HIV-positive tuberculosis patients on antiretroviral treatment in a rural district of Malawi? Int J Tuberc Lung Dis. 2005;9(3):238\_47.
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ. 2007;85(11):867\_72.
15. Edginton M, Enarson D, Zachariah R, Reid T, Satyanarayana S, Bissell K, et al. Why ethics is indispensable for good-quality operational research. Public Health Action. 2012;2(1):21\_2.

**AUTHORS**

**First Author** – Dr. K. Sunil Naik, MD, Assistant Professor, Rajiv Institute of Medical Sciences, Srikakulam, Andhra Pradesh, India.

E-mail ID: - ratna.sree86@gmail.com

**Correspondence Author** – Dr. Kiran Anaparthi, MBBS, [dr.kiran.anaparthi@gmail.com](mailto:dr.kiran.anaparthi@gmail.com), smile4kiran@gmail.com, +919959583830.

**Second Author** – Dr. Kiran Anaparthi, MBBS, In-charge Medical officer, ART Centre, Rajiv Institute of medical Sciences, Srikakulam, Andhra Pradesh, India.

E-mail ID: - dr.kiran.anaparthi@gmail.com

**Third Author** – Dr. Yadlapalli Ratna Sree, MBBS, Medical officer, ART Centre, Rajiv Institute of medical Sciences, Srikakulam, Andhra Pradesh, India.

Table – 2 :- STUDY PROFILE

<b>Period</b>	Jan 15 to June 15
<b>Criteria</b>	Total on treatment as on 01/01/2015
<b>Total Selected population(PLHIV)</b>	3800 for 6 months
<b>Total scheduled appointments</b>	22800
<b>total regular</b>	20822
<b>Total missed</b>	1579
<b>New Miss</b>	1258
<b>Repeat miss</b>	321

**Gender Wise**

1	Missed Schedules	Other Schedules	RR	95% CI	P-value
<b>MALE</b>	636	10764	1.02	0.91 - 1.37	0.70
<b>Female</b>	622	10778	0.97	0.88 - 1.09	0.70
<b>TOTAL</b>	<b>1258</b>	<b>21542</b>			
<b>2</b>	<b>Age group wise</b>				
<b>15-24</b>	126	1956	1.10	0.92 - 1.31	0.28
<b>25-34</b>	445	7637	1.00	0.89 - 1.11	0.95
<b>35-44</b>	461	8095	1.02	0.90 - 1.14	0.76
<b>45-54</b>	181	2969	1.05	0.89 - 1.02	0.56
<b>55-64</b>	34	722	0.82	0.59 - 1.14	0.24
<b>65-74</b>	11	163	1.14	0.64 - 2.02	0.66
<b>TOTAL</b>	<b>1258</b>	<b>21542</b>			
<b>3</b>	<b>Regimen Wise</b>				
<b>ALE</b>	0	6	1.37	0.09 - 19.74	0.81
<b>ALN</b>	1	11	1.44	0.22 - 9.68	0.69
<b>ALN60</b>	0	6	1.37	0.09 - 19.74	0.81
<b>TLATV/r</b>	7	311	0.41	0.20 - 0.86	0.02
<b>TLE</b>	752	9976	1.63	1.14 - 1081	<0.0001
<b>ZLATV/r</b>	0	6	1.37	0.09 - 19.74	0.81
<b>ZLE</b>	56	904	1.06	0.81 - 1.37	0.68
<b>ZLN</b>	442	10322	0.62	0.55 - 0.70	<0.0001

<b>TOTAL</b>	<b>1258</b>	<b>21542</b>
--------------	-------------	--------------

