Original Research Article

A Quantitative Analysis of Treatment Failure Criteria Laid Down by NACO for Suspected Failures of First Line HAART

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ABSTRACT

A rising trend of HIV in new pockets within the country and gradual reduction from high incident states has got attention for consideration of new aspect in HIV treatment, Third line medication. Before starting to implement third line medication, we wanted to analyse the existing criteria for suspected failures and assess for its effectiveness in identification of failures. Out of 3 criteria, we took 2 criteria which can be easily assessed from available date. For the study, we have included all PLHIV who are on treatment for at least 2 years, with criteria 1 to be latest CD4 less than baseline CD4 and criteria 2 to be latest CD4 less than 100 cells/ml. As per study, criterion 1, Latest CD4 <100, 147 patients at 3.01% were identified as failure and as per criterion 2, Latest CD4<Baseline CD4,1128 patients were identified as failures at 23.11% So, the second criteria made it easy for paramedical staff to identify failures more efficiently. The success rate has climbed to 26.13% when both the criterions were used.

Overall failure identified was 1155 failures. Herewith, we deduced that implementation of criteria 2 alone, which is simple to identify, can give maximum number of failures at an early stage of treatment but overall, collective implementation of all criteria can possibly identify maximum possible failures. The failures identified with 2 or more criteria should be given much importance to start in second line HAART to reduce considerable chances of reduced IRIS and to improve living chances for PLHIV with second line medication and further improves chances for use of third line in future and same criteria needed for identification of second line failures also.

*Key words: -*Treatment failure, HAART, Second line treatment, third line treatment, IRIS

INTRODUCTION

By the end of 2017, there were an estimated 21.40 [15.90 - 28.39] lakh people living with HIV (PLHIV) in India. There was an adult (15-49 years) HIV prevalence of 0.22%. Slightly more than two fifths (42%) of the total estimated PLHIV were females. Around 87.58 [36.45-172.90] thousand new HIV infections and 69.11 [29.94-140.84] thousand AIDS-related deaths occurred in 2017. [1] Despite scaling up ART in low- and middle-income countries, an estimated 41% of PLHIV are in need of ART. Universal access to treatment (defined as 80% or greater coverage) is thus still to be achieved in almost all parts of the world. [2] In December 2013, the UNAIDS Programme Coordinating Board called on UNAIDS to support country- and region-led efforts to establish new targets for HIV treatment scale-up beyond 2015. In response,

stakeholder Consultations, new targets have been held in all regions of the world and Powerful momentum is now building towards a new narrative on HIV treatment and a new, final, ambitious, but achievable target of 90-90-90, i.e., by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, 90% of all people receiving antiretroviral therapy will have viral suppression. [3] In recent years, the country has put considerable efforts in expanding HIV-testing sites to detect new infections at the earliest. The HIV prevalence observed among ANC clinic attendees is considered as a proxy for HIV prevalence in the general population, and an estimated 22,677 [10,927-40,605] pregnant women needed ART to prevent mother-to-child transmission of HIV. [4] As a part of sustaining and reaching target of 90-90-90, India has adopted new treatment regimen-third line to counter failures on second line regimen. The criteria laid down by NACO from time to time are much oriented to evolve for easy identification of failures.

Through rigorous efforts by NACO to reduce HIV infections, prevalence rate in general population has come down from 0.33% in 2007 to 0.22% in 2017 [4] but still there are an emerging pocket of infections in the low prevalence states [5] contributing to disease burden in the country. In the state of Andhra Pradesh with emerging new pockets of infection alongside the country, it is of essence to consider alternate path to reach the goal and to verify our current testing and management criteria for easy isolation of failures and to mainstream them for better care and for better virological suppression to make them less transmissible to others.

MATERIALS AND METHODS
Study design: This was a Retrospective Cohort study involving a review of records routinely maintained under the National AIDS Control Programme (NACP) and standard monthly reports submitted by ARTC with cumulative registrations in a financial year. The data collected in white cards as per NACO guidelines were collected to assess the criteria for failures on first line.

Study setting, sites and study population: Srikakulam district with a population of 3.21 million is one of the smallest districts 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 1mobile testing centre) and 1 ART centre with 3 Link ARTC+ and 6 LACs. All HIV-positive persons diagnosed at the ICTC are preferably referred to ART centers for further follow up and treatment and to initiate on HAART. ART centre does regular CD4 tests to assess the progress of the patient and address the issue of possible treatment failures. This enables early intervention and referral to address any failures and to start on second line medication. There have been considerable advances in the treatment prospects in HIV management and it made access to second line very prominent by moving the availability to ART centers and reduced the trouble to already debilitated patients.

NACO has made huge leap in treatment by introducing third line management with raltegravir in the ART program. Our study is aimed at analysing the check points or criteria used to identify the possible failures and to assess the success rate of these points to actually predict the failure and to identify which of the criteria is best to identify with much success and which of the criteria is easy to even paramedical staff to identify failure at the earliest to mobilise for most effective treatment.

The criteria used are 1. Latest CD4 count less than baseline and 2. Latest CD4 count less than 100. The methods used are simple and efficient and calculated based on total patient load at ARTC Srikakulam rather than sample based with at least 2

years of regular medicine and are on active treatment as on Dec 2018 – A launch of Third line treatment. The third criteria of Latest CD4 less than Half of peak value of CD4 during course of treatment is not considered for the study as it requires some assistance and there are increased chances of missing it over time due to heavy work load at ARTC. The criteria selected are simple to identify at paramedical staff level.

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). The total registered patient's records were reviewed for cd4 data and to check adherence issues. The CD4 monitoring box on white card is used along with investigations field in the white card to identify the presumptive failures by paramedical staff based on the criteria. The complete CD4 data was processed to identify the actual failures laid down as per NACO guidelines. Both the criteria are effectively analysed for correctness in most available methods.

RESULTS

The study pointed out the crucial importance of keeping simple criteria for paramedical staff to identify new disease conditions at the earliest. The identification of failures on first line by using the criteria made more efficient when effectively implemented by paramedical team at ARTC. A total of 7026 patients on first line were identified for study, and 2146 patients were not eligible for study as they haven't completed minimum eligibility criteria of 2 years completion of medication. So, total of 4880 were assessed for quantification of criteria.

As per the criterion 1, Latest CD4 <100, out of 4880 patients, 147 patients at 3.01% were identified as failure and 4733 patients at 96.99% were identified as Not failures by this criterion. Likewise, as per criterion 2, Latest CD4<Baseline CD4, out of 4880 patients, 1128 patients were identified as failures at 23.11% and 3752 patients at 76.89% were identified as Not failures. So, the second criteria made it easy for paramedical staff to identify failures more efficiently. The success rate has climbed to 26.13% when both the criterions were used for early identification but stress to be given to criterion 2 for better identification at ART paramedical level.

The most interesting aspect of the study was, as per criterion 1, total of 147 failures were identified of which, 120 failure were also recognised by criterion 2,additionally only 27 more failures were identified by first criteria against Criterion 2. Considering Criterion 2, which identified 1128 failures of which 120 were also identified by criterion 1 and additionally, a total of 1008 more failures were identified.

Table 1:-Criterion 1 VS Criterion 2

Criteria 1 Vs Criteria 2	FAILURE in Criteria 2	NOT FAILURE in Criteria 2	NOT ELIGIBLE in Criteria 2	Grand Total
FAILURE in Criteria 1	120	1008		1128
NOT FAILURE in Criteria 1	27	3725		3752
NOT ELIGIBLE in Criteria 1			2146	2146
Grand Total	147	4733	2146	7026

DISCUSSION

This is one of the studies conducted in India with important aspect to look at criteria laid down in national health program in identifying treatment failures. NACO, a monitoring organisation in India that look after HIV program has recently introduced third line of treatment in ART program to effectively control the emergence of viral resistance and to enhance the livelihood of people living with HIV/AIDS. This study started with linking data from registered PLHIV at ARTC, RIMS, Srikakulam at par with census data and assigning census codes issued by Govt. of India to villages and towns in Srikakulam [5] and then consolidated for the period of study, i.e., April 2008 to Dec 2018 for 10 years, to assess treatment failures based on criteria laid down by NACO from time to time. In

the study, it showed there was dramatic increase in treatment failures and current failure rate was more than 27%. Among 3 criteria, we have assessed 2 criteria against each other to identify best criteria which when used by paramedical staff with high success rate. A recent study estimated a relatively high rate of patients in virological failures, while among them has an important proportion harboured with wild-type viruses and this highlights a real need to reinforce treatment adherence [7] as PLHIV who are regular on HAART has reduced chances of transmitting virus to general population [8] and this early initiations on HAART in asymptomatic stage has led to improvement in treatment adherence which can potentially reduce wild strains in virus in future. The decline in HIV cases registrations was correlated with increase in eligibility criteria for initiation on HAART [9] and regular on treatment patients has low risk of transmitting the virus.

A key finding of this study is that, the treatment failures are best identified with second criteria alone and is considered best, easy and most versatile to identify failures. The First line treatment was aimed at achieving best virological suppression and improvement in cd4 count which eventually lead to better survival of PLHIV. The regimen of choice used was with a backbone and ideal drug, Lamivudine, with less side effects and less resistance profile. This first line regimen uses other NRTI, zidovudine or Stavudine or Tenofovir, as second NRTI to reduce chances of resistance to the lamivudine. The first line regimen was completed with use of NNRTI, Nevirapine or Efavirenz, as third drug of the regimen. The combination of 2 NRTIs + 1 NNRTI as first line regimen gave a great success to Indian HIV/ ART program as free HIV treatment. It was most effective in both cost and success ratios.

The Second line regimen of the guidelines [10] made entry to the country as the use of first line regimen has led to emergence of resistance to HAART and showing isolated incidences for drug resistance. This progressively led to adaptation of second line medication to counter the resistance. Atazanavir (ATV) was licensed in 2004 as the first PI on the market for once daily administration. In treatment-naïve patients, atazanavir was compared to many other agents. Both boosted and upboosted atazanavir proved as effective as efavirenz [13] or nevirapine. [14] Two large phase III trials investigating QUAD on therapy-naïve patients led to the approval of TDF+FTC+atazanavir/r. In 236-0102, 700 patients received either TDF+FTC+atazanavir/r, or TDF+FTC plus efavirenz (Sax 2012) and in 236-0103, 708 patients were treated with either TDF+FTC+atazanavir/r. [15] After 48 weeks, 88% under TDF+FTC+atazanavir/r (versus 84%) and 90% (versus 87%), respectively, achieved a viral load below 50 copies/ml. This convinced for use of PI based regimen as alternate to counter resistance and used as second line regimen who are convinced as best for second line treatment in India.

The emergence of resistance along with progressive increase in viral loads for patients on second line gradually raised the need for third line medication. In FLAMINGO, GS103 and ACTG 5257, the integrase inhibitors were also tested against boosted PIs such as atazanavir/r or darunavir/r. [16] Dolutegravir and raltegravir were superior, mainly with regard to tolerability. In the three-arm study ACTG 5257, however, atazanavir was inferior to raltegravir and darunavir in a tolerability endpoint. Atazanavir was also inferior to darunavir in the combined efficacy/safety endpoint. [17] Combined with all the studies, most of the studies showed the tolerability, safety, and efficacy of darunavir and raltegravir are far superior to all the regimens available so far under national program. So, the introduction of these drugs under program can have major benefits to counter resistance and let PLHIV use the medication to the best of their efforts. We also adhered to the guidelines for reporting of observational studies [11] and ethics [12] to

come to provisional understanding on the criteria.

CONCLUSION

In Srikakulam, a small district of Andhra Pradesh, state of India, wherein a reduction of 10.32% in new cases for recorded in financial year 2017-18 at par with national standards and continuing previous years trend of decreasing spread of the infection in the district. The new policy of third line regimen in treatment of HIV patients was introduced to counter the raising failures on first line treatment and second line. The study gave a conclusive evidence that the criteria laid down to identify failures are best and 2 criteria alone can identify 27% of failures over period and can be done even at paramedical staff. The criteria are so simple that basic literate PLHIV can identify them and can keep a check on his treatment progression. So far, Atazanavir and Lopinavir in boosted condition has given much second line support to first line failures, now, with introduction of third line with Raltegravir and Darunavir, the treatment of PLHIV has gone to next level and this transition will not be affected as the criteria for identification won't change and the staff are well versed. This successful criterion will help India to reach good virological suppression among all PLHIV with first line, Second line, and upcoming third line and will enable India to reach 90-90-90 target.

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