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Treatment Outcome of Second line ART in PLHIV

Medicine

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KEYWORDS:

Introduction:

The patients initiated on Antiretroviral treatment (ART) and if adherence is good can continue on first line ART for a number of years. However, over the years some percentage of People Living with HIV(PLHIV) on first line ART develops resistance to these drugs due to mutations in virus. Patients suspected of treatment failure on first line ART based on WHO defined immunologic, clinical and definitive virologic failure qualify for switch to second-line ART. With the increase in number of patients on first line therapy it is envisioned that a proportion of patients will experience treatment failure and need second line ART regimens over time. In 2008, National AIDS Control Organization (NACO) piloted a national strategy for the provision of free second-line ART in India and these drugs are being provided free of cost at 10 Centres of Excellence and their linked ART Plus Centres. As on August 2015, 12,823 patients were receiving second line drugs in the National programme [1].This study was done to observe the clinical, immunological, virological and survival of patients on second-line ART under programmatic condition.

Materials and Methods:

Study site: This observational study was conducted at the ART Centre of the Centre of Excellence (COE),Gandhi Hospital, Secunderabad. The ART centre is one of the largest in this region with 14,024 PLHIV registered in HIV care and 5,076 currently on first line ART.COE is also a referral centre for evaluation of patients suspected of first line failure from 7 other ART centres.

Study population: Data of all patients >15 years of age who were started on second-line therapy due to failure of first line ART at COE Gandhi Hospital during JAN2013 to December 2013 were included in this study. The first line regimen recommended by NACO and received by patients was Zidovudine + Lamivudine + Nevirapine if hemoglobin was >9gm/dl or Tenofovir+Lamivudine + Nevirapine if hemoglobin <9gm/dl. Efavirenz was substituted for Nevirapine in those taking anti-tubercular drugs and those with Nevirapine toxicity.

Patients on first line therapy were eligible for evaluation for second-line ART if they had been receiving ART for at least 6 months, and had demonstrated treatment adherence of >95 %, and had WHO clinical or immunological failure as per NACO guidelines. Viral load estimation was done in these patients and those with HIVRNA >5,000 copies/mL (Oct 2010) were considered as first-line failure and started on second line therapy [2].In March 2014, the cut off level of viral load for starting ART was reduced to >1000 copies/ml by NACO.

All patients with first line failure between JAN 2013 and DEC 2013 were given a uniform second-line ARTregimen provided by NACO comprising of Tenofovir (TDF) + Lamivudine (3TC)+ Atazanavir/ ritonavir (ATV/r). Tenofovir (TDF) replaced by Zidovudine (AZT)if patient not taken Zidovudine (AZT) in previous history and Hemoglobin >9 g/dL. Atazanavir/ritonavir (ATV/r) replaced by Lopinavir/ritonavir (LPV/r) in patients with significant hyperbilirubinemia (serum total Bilirubin is > 7 mg/dl or the Child-Pugh Score is ≥ 7)or HIV-2.In patients with concomitant tuberculosis rifampicin was replaced by rifabutin without any change in the ART regimen

PLHIV were followed up monthly and CD4 count was done 6 monthly for all patients. During each visit, patients were counselled for adherence and evaluated for drug toxicity, clinical improvement and opportunistic infections. Patient's weight, clinical stage, functional status, drug toxicity, adherence to ART medication, presence of opportunistic infection, any change in therapy were documented. Viral load (VL) was repeated by COBASTaqMan HIV-1 assay in all patients at 6 months, if itwas<400copies/ml at 6 months it was not repeated further as per National guidelines. Patients with VL >400copies/ml at 6 months, adherence was reinforced and VLwas repeated at 12 months. Adherence was calculated on the basis of pill count at every visit by the formula: Number of pills actually taken by a patient for a particular time period/Number of pills prescribed for this time period × 100. For analysis we compared those with >95 %adherence at every visit with those with <95 % at any visit. At the end of the month patients were labelled as 'ontreatment' if they picked up their drugs, 'missed' if they did not pick up drugs for the month, 'dead' if they expired and 'transferred out' if they were transferred out to another ARTcentre. Those patients who did not come for 3 consecutive months were labelled as 'lost to follow up (LFU)'at the end of fourth month as per NACO guidelines.

Results:

One twenty four patients were started on second line ART (TDF/ZDV+3TC+Atv/Rtv) between January 2013 to December 2013. At the end of follow up, out of 124 patients started on second line therapy, 17 (13.7%) had expired.The most common cause to switch on second-line ART was combined immunological and virologic failure.

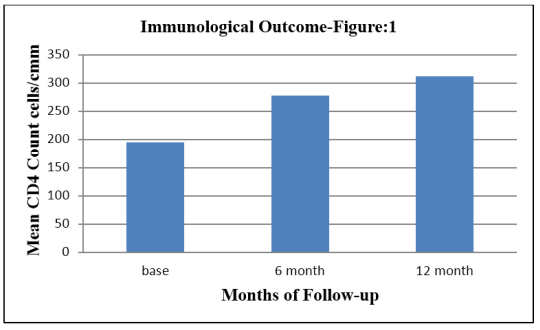
Outcome on second line therapy:

Immunological outcome (Figure:1):

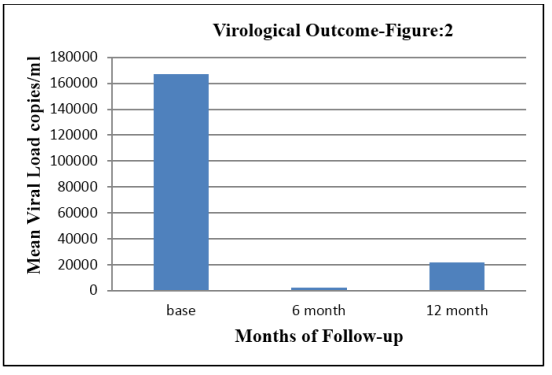
There was a significant increase in mean CD4 count at 6 months and 12 months as compared to baseline.

Virological outcome (Figure:2):
A significant decrease in mean PVL was observed at 6 months and 12 months. 73(64.60%) patients achieved virological suppression at 6 months and 87(81.30%) at12 months.

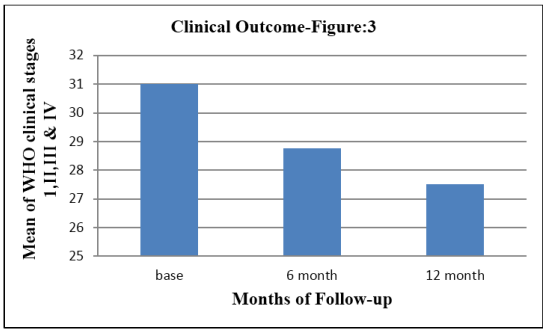
Clinical outcome (Figure:3):
Second-line ART significantly increased mean body weight of patients at 6 and 12 months of treatment. Second-line ART reduced the number of patients 61(49.19%) from WHO clinical stages II,III & IV to 21(19.62%) during 6 months & 12 months treatment follow-up.



When we observed mean CD4 count of patients from baseline (at starting of second line) to 12 months, it is gradually increasing.



Viral load of some patients slightly increased at 12 months, it may due to poor personal habits (tobacco, smoking, and alcohol), WHO clinical stage III & IV conditions, malnutrition, low baseline CD4count and high PVL, baseline drug resistance prior to starting secondline treatment, duration of secondline treatment prior to starting secondline ART in the NACO programme, were associated with poor treatment outcome in terms of failure to achieve virological suppression even after 12 months treatment follow-up.[Table 3].



When we observed clinical stage of patients from baseline to 12 months, it is gradually decreasing. Many people who are under WHO clinical stage iv,iii,ii & 1condtions at the time of second-line initiation are came down to stage i after 12 months of second line art treatment.

Discussion: This observational study reports the outcome of patients receiving secondline antiretroviral therapy under the National AIDS control programme of India. As the extent of HIV/AIDS treatment in developing countries continues, and the number of patients switching from first-line to second-line therapy will inevitably increase.Our study shows an analysis describing the outcomes of 124 patients on second-line ART regimen for 12 months treated at tertiary care hospital in Hyderabad, Telangana state, India. In this observational study there was good clinical outcome as well as immunological improvement in patients starting second line therapy under programmatic conditions in India.

At the time of second line ART initiation, theCD4 count was lower and PVL was higher in our study as compared to similar studies done at Thailand[3] and SouthAfrica[4,5].Treatment failure (PVL more than 400 copies/ml) showed that low baseline CD4 count, WHO stage (III/IV) and poor treatment adherence history were associated with high incidence of treatment failure.

One study from Malawi on second-line treatment in a prospective observational study showed higher numbers of virological suppression after 12 months of second-line therapy[6]. Another study from South Africa, in which the frequency of virological monitoring was the same as in our cohort, similar proportions of patients reaching virological suppression ,400 copies/ml were seen after one year of second-line ART in on-treatment analyses [7,8].

This observational study reflects the actual efficacy of second-line ART in our cohort, in which regular Immunological &virological monitoring is routine clinical practice.Our study analysis showed that 87 (81.3%) had adequate virological response at one year. Similar results were observed in studies from other RLS settings [9, 10], while a study from Africa has shown adequate virological suppressionin 86 % of patients at 96 weeks with the WHOrecommendedsecond line regimen of NRTI and boosted PI[11].High viral load at baseline and poor adherence during second line therapy was an important risk factor for virological failure in our study similar to other studies [12,13,14,15].

In most of the second-line ART efficacy studies in RLS, a cut-off point of plasma viral load, <400 copies/ml was used to define an adequate virological response. However, in developed countries,a more strict value (PVL - <50 copies/ml) is generally used to define virological suppression [16]. Low-level viremia, (PVL range between 50 to 400 copies/ml) may indicate on-going viral replication and could therefore lead to the selection of drug-resistance mutations and subsequent virological failure.

There are some limitations to this study. First, as it is a retrospective observational study, there may be unmeasured underlying determinants influencing results. Second, there were some missing data, mainly due to died patients. Unfortunately, causes of death in these patients were unknown. In our study 11% of patients died over the follow-up, including four patients died within 6 months after the switch.

Even after 12 months follow-up high viral load is seen in some patients. As a result, persisting low-level viral replication may occur in some patients. It remains to be seen whether this is of clinical relevance in PI-based regimens. However, the long-term efficacy in clinical practice of this strategy remains to be seen[17]. Regular virological monitoring is necessary to detect treatment failure before immunological deterioration occurs.Increasing the accessibility of viral load testing as recommended by the recent WHO guidelines would definitely go a long way in improving the second line program.

The number of people receiving antiretroviral therapy (ART) in resource limited settings is rapidly increasing, at the same time the number of First-line ART treatment failure cases also climbing rapidly. Looking at this scenario from a programmatic view, we can categorize the patients into two broad groups, One group of that patients whose First-line ART treatment failure is due to drug resistance. Therefore making it necessary for that group to be switched to a second-line regimen. The second groups of patients are

those who though non-adherent, have not yet developed resistance to the First-line regimen. Therefore they may be continued on the same first-line regimen.

A number of studies found that, viraemia on first-line therapy can be reversed with adequate adherence support [18,19] and it is help to preserve the use of second line drugs, which is an important objective given that therapeutic options beyond second line are very expensive and poorly available in RLS.

Conclusion: Our analysis found a virological failure on antiretroviral therapy can be due to a number of factors, including baseline drug resistance among patients prior to starting treatment, the evolution of drug resistance during treatment, duration of time on treatment, and poor adherence to medication. This study recommends the greater access to virological monitoring when it is required in RLS order to detect virological failure and implement more intensive adherence counselling prior to the development of resistance mutations.

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