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Profile of HIV Patients on Second Line Antiretroviral Therapy: The Indian Experience

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Abstract

Background: The proportion of patients on second line in resource limited settings are estimated between 1-5%. The present study describes the profile and outcomes of Indian patients receiving second line ART.

Methods: Information on HIV patients on second line ART was gathered. Socio demographic data, probable transmission route, baseline clinical parameters and comorbidities during therapy are studied along with first-line ART regimen initially introduced, its adherence and the reason for switch and components of the second-line ART regimen.

Results: Out of the total 2174 HIV patients 53% were on first line ART and of these 51 patients on second line ART were studied. The average time of initiation of first line ART was 17.67 months with median of 2 months whereas switch to second line ART was in 53.75 months with median of 60 months. Almost 71% of the patients on second line ART had been diagnosed with HIV infection with low CD4 count of <200. However 54%, 67% and 58% patients show more than 50% rise in their CD4 count post switch to second line after 3, 6 and 12 months of treatment which is a substantial improvement. Twenty-five per cent of patients showed non adherence. Tenofovir based regimens had a slight advantage with lesser number of side effects being reported.

Conclusion: Early diagnoses of infection, early initiation of ART and drug adherence are the cornerstones for success in managing HIV patients. Understanding the profile and drug resistance pattern is necessary for ensuring effective and long term survival.

Keywords: Antiretroviral therapy; Human immunodeficiency syndrome; Tenofovir; Drug adherence

Introduction

Over the past three decades, the adverse effects of Human immunodeficiency virus (HIV) infection and its progression to AIDS have been reflected in various regional and global health statistics. The greatest impact of HIV/AIDS is seen in resource-limited settings and about 70% of the global population of HIV-infected individual's lives in sub-Saharan Africa [1]. The rapid scale-up of antiretroviral therapy (ART) in resource-limited settings over the past decade has resulted in substantial reductions in morbidity and mortality [2-4] and increased life expectancy [5] for people living with HIV/AIDS. In June 2011, governments committed to a target of reaching 15 million people with antiretroviral treatment (ART) by 2015 at the United Nations High-level Meeting on HIV/AIDS [6]. If this target is met, UNAIDS - the Joint United Nations Programme on HIV/AIDS estimates that up to twelve million infections and more than seven million deaths can be averted by 2020, and that the number of new infections could be reduced by more than half by 2015 [7]. The massive global expansion of access to HIV treatment has transformed not only the HIV epidemic but the entire public health landscape, demonstrating that the right to health can be realized even in the most trying of circumstances [8]. Antiretroviral therapy (ART) in resource-limited settings has expanded in the last decade, reaching >8 million individuals and reducing AIDS mortality and morbidity. The last decade has seen a 50% decline in the number of new HIV infections [9]. While the National AIDS Control Organisation (NACO) estimated that 2.39 million people live with HIV/AIDS in India in 2008-09, [10] a more recent investigation by the Million Death Study Collaborators in the British Medical Journal (2010) estimates the population to be between 1.4-1.6 million people [11]. 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 [12]. But over the years patients with antiretroviral treatment (ART) failure are increasingly encountered in resource-limited settings [13-15]. A number of patients can be expected to develop drug resistance to first-line regimens, and a growing number of patients on ART in developing countries have switched to second-line therapy [16-18]. The proportion of patients on second line in resource limited settings are estimated between 1-5% [19-20]. In India as per NACO a total of 300,743 HIV patients are on first line ART and NACO envisages that nearly 3,000 patients, have become resistant to first-line therapy, and put on second-line ART. For patients failing second-line therapy, treatment options are largely nonexistent. Current WHO guidelines provide some guidance for treatment in the case of second-line failure, but these are prefaced with the caveat that many countries have financial constraints that will limit the adoption of third-line options. Thus, there is a need to understand the profile of HIV patients on second-line regimens in resource-limited settings in order to both limit its occurrence and forecast the need for treatment options beyond second-line. The aim of the present study is to describe the profile of all the HIV patients on second line ART in a tertiary care hospital.

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Methodology

The data were obtained retrospectively from the HIV patients on second line ART taking care and treatment from a tertiary care hospital. Data was gathered by triangulation of information from detailed case sheets of the patients and registers, information obtained from dermatology department and the immunodeficiency centre. The patients presenting with HIV infection are registered and separate case files are maintained for each patient. Data of a total of 53 patients who were switched from first line ART to second line ART were retrieved. Socio demographic data including age, education, marital status and probable transmission route were documented. Baseline clinical parameters and co-morbidities during therapy were studied along with first-line ART regimen initially introduced, its adherence and the reason for switch and components of the second-line ART regimen. Biochemical parameters were also noted. CD4 count at diagnosis and when put on first line ART, at time of switch to second line ART, post 6 months and 12 months of second line ART were noted.

Case definitions

The following case definitions were applicable for switch to 2nd line ART:

- Virological failure: HIV RNA concentration (viral load) of 1000 copies/ml (i.e.,3.0 log10 copies/ml) on two consecutive occasions after at least 6 months of treatment.
- Immunological failure: decrease in CD4 cell count to pre-therapy baseline level (or below); 50% decrease from the peak value during treatment; and persistent low CD4 cell counts of less than 100 cells/mm3 after at least 12 months of ART.
- Clinical failure: occurrence of a new WHO stage III or IV opportunistic disease while on treatment.
- Treatment failure: Presence of either of of virological, immunological or clinical failures.

For the purpose of this study, a CD4 cell count increase ≥50% of the value after the switch was regarded as a 'good immunological response' to second-line ART.

- ART non-adherence: Non adherence was defined as <95% of drug intake over the duration of each month.

Statistical analysis

Categorical variables were expressed as proportions. Continuous variables were described using means± standard deviation (SD) and in terms of median (range) for skewed data. The reliability of the parameters were given by 95% confidence interval (CI). Statistical analysis was carried out in SPSS 14.0.

Results

Information on 2714 male HIV patients was gathered. The mean age of these patients was 35.52 years + 6.89 years. Of these almost 53% (1438) HIV patients were on first line ART treatment. Information was extracted for 51 patients who were on second line ART and analysed in detail. The mean age was 40.58 ± 8.57 years. Majority of the patients (96.1%) were married. Education levels revealed that 17% had studied only till the 5th standard, 63.4% of the patients had passed their 10th grade and almost 10% each were 12th class pass and graduates. The mean weight was 61.53 ± 8.78 kgs (Range=3) and mean BMI 21.30 ± 2.71. Minimum BMI was 14.16 and maximum was 27.74. Table 1 shows the probable mode of transmission, presenting symptoms and CD4 counts in this cohort of patients, in addition to all above socio demographic data. More than half of patients had heterosexual route of transmission and 1 contracted HIV through blood transfusion. Three patients were diagnosed after contact tracing.

Characteristic	n (%)	95% CI
Probable mode of transmission		
Heterosexual	28 (54.9)	41.16- 68.09
Unknown	22 (43.1)	30.10- 56.92
Blood Transfusion	1 (2.0)	0.10- 9.29
Symptoms at diagnosis*		
Opportunistic infection (OI)	27 (52.9)	39.26- 66.28
Weight loss, loose motion and fever	13 (25.5)	14.97- 38.72
Herpes Zoster	4 (7.84)	2.54- 17.84
Contact tracing	3 (5.9)	1.51- 15.17
Donor	2 (3.9)	0.66- 12.35
Diss koch's	2 (3.9)	0.66- 12.35
Reasons of starting second line ART*		
OIs	33 (64.6)	50.93- 76.85
Asymptomatic with low CD4 count	10 (19.6)	10.41- 32.17
Symptomatic with low CD4 count	8 (15.7)	7.56- 27.61
High Viral Load	1 (2.0)	0.10- 9.29
Time in months from diagnosis to first line ART		
Mean (SD)	17.67 (40.69)	
Median (Range)	2 (0-165)	4.10-31.24
Time in months from diagnosis to second line ART		
Mean (SD)	53.75 (27.97)	
Median (Range)	60 (3-109)	44.43- 63.08
CD4 cells/ml at diagnosis		
<50	9 (17.6)	
50-200	27 (53.0)	
200-350	8 (15.8)	
350-500	4 (7.9)	
≥500	3 (5.9)	
Mean (SD)	153.40 (111.26)	91.78-215.02
CD4 cells/ml at first line ART initiation		
<50	7 (13.8)	
50-200	40 (78.4)	
200-350	4 (7.8)	
350-500	0	
≥500	0	
Mean (SD)	80.47 (64.44)	44.78-116.15
CD4 cells/ml at 2nd line ART switch		
<50	10 (19.6)	
50-200	38 (74.5)	
200-350	2 (3.9)	
350-500	0	
≥500	1 (2.0)	
Mean (SD)	110.93 (98.53)	57.47-164.40

*Multiple responses

Table 1: Socio demographic and CD4 distribution in HIV patients.

Around 53% of the patients had opportunistic infections (OIs), while 25.5% had weight loss and chronic diarrhea with fever at time of diagnosis. Treatment for OIs was the reason for diagnosis of HIV in more than 50% of the patients. Presence of OI was also the main reason for start of second line ART in 65% of patients. The average time from diagnosis to first line ART was 17.67 months and from diagnosis to second line ART was 53.75 months. At the time of diagnosis of HIV the median CD4 count was 119 cells/mm^3 with 70.6% of patients having low CD4 count of ≤ 200 cells/ mm^3. At the time of first-line ART failure, the median CD4 count was 65 and at the time of second line ART failure it was 52 cells/mm^3. 54% (95%CI=38.77, 67.47), 67% (95%CI=52.02, 67.47) and 58% (95%CI=43.07) patients had more than 50% rise in their CD4 count post switch to second line after 3, 6 and 12 months of treatment (Figure 1). Table 2 gives the details of CD4 with respect to various stages of treatment. The details of past and current OIs are given in Table 3. Around 68.6% of the patients had some past infection

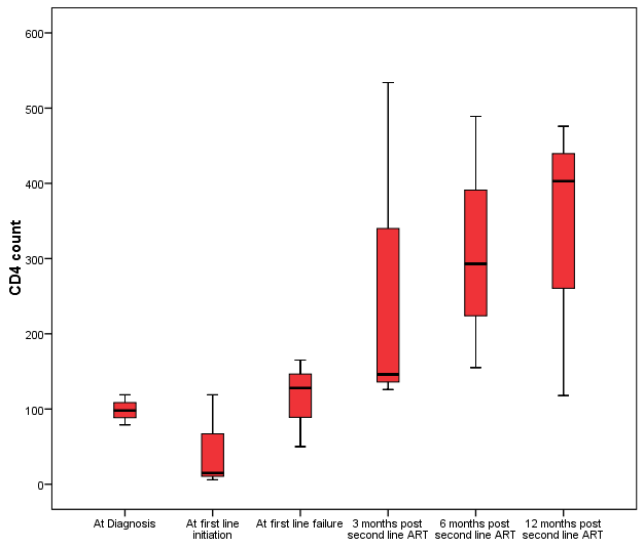

Figure 1: CD4 distribution at various stages of treatment.

Stage of treatment	CD4 cell count (cells/mm3), median (range)	Patients with ≥50% rise in CD4 count post switch to second line ART n(%)**
At time of diagnosis	119 (29-388)	-
At start of first line ART	65.0 (6-246)	-
Switch to second line ART	52.0 (2-415)	-
3 months post treatment	57 (10-524)	24 (54)
6 months post treatment	142 (40-600)	30 (67)
12 months post treatment	312 (50-476)	26 (58)

** Denominator is 45 as 6 patients went on second line ART in 2013 for whom post 3, 6 and 12 months measurements are not available.

Table 2: Distribution of CD4 count as per stage of treatment.

	Past OIs	(%)	Current OIs	(%)
Tuberculosis	19	37.25	5	9.80
Herpes Zoster	8	15.69	2	3.92
Palm Koch's	4	7.84	0	0.00
Hepatitis B (Acute)	1	1.96	1	1.96
Lymphadenopathy	2	3.92	0	0.00
Pleural effusion	1	1.96	0	0.00

Table 3: Details of past and current opportunistic Infections (OIs).

and currently there were 17.65% of patients suffering from OIs. One hundred percent of the patients had counseling from trained counselor prior to start of first line as well as second line ART and majority (69%) has atleast 2 sessions with the counselors. Adherence was reinforced by the counselor highlighting its importance in every visit. 25% of patients showed some form of non-adherence over the last six months.

Drug regime

The preferred first line therapy was Zidovudine, Lamivudine and Nevirapine in most patients. Patients on concomitant ATT were on Efavirenz instead of Nevirapine. Few patients were also given Tenofovir, Lamivudine/ Emtricitabine and Efavirenz as first line therapy. The favoured second line therapy was introduction of Protease inhibitors mainly Lopinavir boosted with ritonavir instead of NNRTIs. Following first line treatment failure, a total of 16 patients had a treatment modification after failure. All the patients (n=10) who showed failure to drug zidovudine were switched to either Nevirapine or 3TC.

Adverse effects to second line therapy were seen mainly in the form of anemia and dizziness in 11 (2.16%) patients which were mostly associated with Lopinavir boosted with ritonavir.

Discussion

A growing proportion of patients on antiretroviral therapy in resource limited settings have switched to second-line regimens [21]. Failure of first-line antiretroviral therapy is inevitable sooner or later in a proportion of patients. Access to second-line antiretroviral therapy regimens in developing countries is limited by the expense of second-line treatment, mainly due to the inclusion of protease inhibitors [22,23]. The present study was carried out to understand the profile of HIV patients on second line ART in India. The mean age of patients was 40.58 ± 8.57 years. The mean weight was 61.53 ± 8.78 kgs (Range=3) and mean BMI 21.30 ± 2.71 which is comparable to studies on second-line therapy in sub-Saharan Africa and Asia [24,25]. Heterosexual transmission was the main mode of contracting infection in 55% of HIV patients. The average time of initiation of first line ART in our study was 17.67 months with median of 2 months whereas switch to second line ART from first line ART was 53.75 months with median of 60 months. Almost 71% of the patients on second line ART had been diagnosed with HIV infection with low CD4 count of <200. Research has shown that low CD4 count at baseline or diagnosis is independently associated with a increased hazard failure on first line and death [24]. The average time from first-line ART initiation to switch in a Nigerian cohort was about 17 months [25]. In various other studies, the duration of first-line therapy in patients switching to second-line ART has been reported to range from 11 to 35 months [25-30]. The fact that a large majority of patients requiring a switch to second line therapy are those having a low CD4 count at time of diagnosis: it is imperative that all out efforts are made to diagnose this infection as early as possible and therefore reduce the burden on the second line drugs. All first line regimes used in patients included in the study were based on WHO or NACO regimes and have proven to be very efficacious. WHO recommends a combined therapy of 2 NRTIs with an NNRTI as the initial first line regimen. However in most countries, tenofovir based regimens have taken over as first line therapy. The tenofovir based regimens have the advantage of better efficacy, lesser drug resistance and lesser number of side effects.

Our study found 54% (95%CI=38.77, 67.47), 67% (95%CI=52.02, 67.47) and 58% (95%CI=43.07) patients having more than 50% rise in their CD4 count post switch to second line after 3, 6 and 12 months of treatment which is a substantial improvement.

In most adults and children, CD4 cell counts rise when ART is initiated and immune recovery starts. Generally, this increase occurs during the first year of treatment, plateaus, and then continues to rise further during the second year [31]. However, severe immunosuppression may persist in some individuals who do not experience a significant rise in CD4 cell count with treatment, especially those with a very low CD4 cell count when initiating ART. Failure to achieve some CD4 recovery should alert the health care provider to potential adherence problems or primary non-response to ART, and consideration should be given to continue prophylaxis for opportunistic infections such as co-trimoxazole preventive therapy.

Non adherence is one of the main reasons for failure of first line ART. In fact it is the second strongest predictor of progression to

AIDS and death, after CD4 count [4-6]. Incomplete adherence to ART is common in all groups of diseased individuals. The average rate of adherence is approximately 70%. It is a well-known fact that long-term viral suppression requires a near-perfect adherence to ART. The resulting virologic diminishes the chances of for long-term clinical success. Non-adherence is therefore a major factor in undermining the dramatic improvements in HIV-related health parameters seen in countries where ART is widely available. In our study, 25% of patients showed non adherence. The various reasons for non-adherence included non-availability of one or the other drug at sometime, forgetfulness, low motivation levels, adverse effects of drugs and ill health. Being away from home 68.8%, being too busy 58.9%, forgetting 49.0%, having too many medicines to take 32.6% and stigma attached to ARVs 28.9% were the reasons suggested in a study from Kenya [32]. There is hence a felt need for multiple-target interventions to resolve these barriers to adherence.

Thus continued success of ART programs will require understanding the emergence of HIV drug resistance patterns among individuals in whom treatment has failed and managing ART from both an individual and public health perspective [32]. With growing numbers of people in developing countries having been on treatment for a decade or even longer, ensuring the effectiveness of treatment, and long-term survival, depends on continuous access to newer and more potent ARVs.

Conclusions

Failure of first-line antiretroviral therapy is inevitable sooner or later in a proportion of patients. Access to second-line antiretroviral therapy regimens in developing countries is limited by the expense of second-line treatment, mainly due to the inclusion of protease inhibitors. The average time of initiation of first line ART in our study was 17.67 months with median of 2 months whereas switch to second line ART from first line ART was 53.75 months with median of 60 months. Almost 71% of the patients on second line ART had been diagnosed with HIV infection with low CD4 count of <200 which may have independent association with failure on first line ART. Non adherence is one of the main reasons for failure of first line ART where in our study, 25% of patients showed non adherence. Our study showed that tenofovir based regimens had a slight advantage with lesser number of side effects being reported. Early diagnoses of infection, early initiation of ART and drug adherence are the cornerstones for success in managing this enemy of human survival. Thus it is important to understand the profile, the HIV drug resistance pattern in HIV patients who have failed on first line for ensuring effective and long term survival.

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