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Factors leading to failure of firstline anti retroviral therapy (ART); a retrospective study in indian teritiary care government settings

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ABSTRACT

Background

HIV is a lenti virus that causes HIV infection in humans in which progressive failure of immune system allows life threatening opportunistic infections and cancers to thrive. So it is important to study the factors that lead to failure of first line ART.

Aims and Objectives

To find out the factors leading to failure of first line ART like socio-demographic factors, clinical factors, immunological factors, virological factors etc.To assess the CD4 count in subjects using first line and second line ART. To assess the viral load in subjects who failed first line ART.

Methodology

Retrospective cohort observational study was conducted to assess the factors leading to the failure of first line ART. HIV patients who met inclusion criteria were informed consented and included in the study and relevant data was collected in a prior designed data collection form.

Results

In our study we found that controls were more among 30-40 yrs age. Males and females were equally distributed in cases and controls. Widowed females were found more among cases. Illiterates were found more among cases than controls. Cases children were more HIV seropositives than controls. Cases were more in WHO stage-4 clinical staging than controls. Cases had more number of drug substitutions, drug related adverse effects, low medication adherence, more number of LFUS and hospitalisations than controls. Cases were more in number who travels more than 60 minutes and more time gap between diagnosis and time of ART initiation and cases had raised RFTS, LFTS, and lipid profile at time of treatment failure. Cases had more serious opportunistic infections than controls.

Conclusion

From our study we found that marital status, illiteracy, labour work, low income status, loss of follow up's, wrong diagnosis of type of HIV virus initially that lead to the wrong treatment, positive family history of HIV,

recurrent stage 3, 4 infections, more no. of drug substitutions, zidovudine, stavudine based regimens, long time gap between diagnosis and ART initiation, long travel time to ART centre, more no. of drug related problems, more no. of recurrent opportunistic infections, more no. of hospitalisations, raised RFT's, LFT's, Lipid profile, lower adherence levels, low CD4 counts on long term use of ART were considered as factors that lead to first line ART failure.

Keywords: CD4 Count, Virologic failure, Immune system, ART failure, Opportunistic infections.

INTRODUCTION

Centres for Disease Control and Prevention (CDC) defines that a person with HIV is the one who have positive antibodies to Human Immunodeficiency Virus (HIV),with CD4 count <200 cells/mm3 with or without any one of the AIDS defining illness i.e., opportunistic infections [2]. There are two HIV types, HIV-1 and HIV-2. HIV-1 is the most prevalent type throughout the world [3]. Globally, 36.7 million people were living with HIV at the end of 2016. An estimated 0.8% of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions [4]. Among the states/ union territories in India, in 2015, Andhra Pradesh & Telangana has shown the HIV prevalence of 0.66% [5]. HIV can be transmitted through blood, sexual contact, or injection drug use and from mother to child (also known as perinatal or vertical transmission) [6]. WHO staging system groups HIV progression into four clinically relevant stages. The CD4 count and viral load are two measures of the prognosis of HIV. When HIV infects CD4 cells, actively multiplies and kills CD4 cells- a specific type of white blood cell-that are the immune system's key infection fighters the effects of HIV are measured by the decline of the number of CD4 cells [6]. The CD4 count is the number of CD4 cells in the blood and reflects the state of the immune system. The normal CD4 count in a healthy adult is between 600 and 1200 cells/mm^3. When the CD4 count of an adult falls below 200 cells/mm^3, the risk of opportunistic and serious infection is high [6]. Viral load is the amount of HIV virus in the blood. The test is used as a marker of response to antiretroviral (ARV) treatment [8]. the viral load is very high shortly after primary infection. It falls steeply when the body develops antibodies and rises after a number of years as the CD4 count drops. High viral load leads to higher transmission risk [6]. viral load is a marker of response to ART. A patient's pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression. The key goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART [8].

NEED OF THE STUDY

Infection with the Human Immunodeficiency Virus (HIV) and its progression may leads to depletion of the immune system and increases the risk of opportunistic conditions which are responsible for increased morbidity and mortality. Antiretroviral therapy (ART) will help the patient in restoring their immune function by reducing the viral load and by increasing the number of CD4+ T cells. On the other hand failure of first line ART will make the patient immune system much weaker. So many number of known and unknown clinical, immunological and socio demographic factors will take part in the failure of first line ART. Identifying and controlling those factors will be help in maintaining the clinical condition of the patient and thereby reducing morbidity and mortality. Entifying and controlling those factors will be help in maintaining the clinical condition of the patient and thereby reducing morbidity and mortality.

AIM AND OBJECTIVES

Aim

To study the factors leading to failure of first line ART.

Objectives

To find out the factors leading to failure of first line ART like Socio-demographic factors, Clinical factors, Immunological factors, Virological factors**,** to assess the CD4 count in subjects using

first line and second line ART, to assess the viral load in subjects who failed first line ART.

METHODOLOGY

Study Design

Retrospective cohort observational study was conducted to assess the factors leading to failure of first line ART.

Study Period

The study was conducted within a time period of 6 months i.e., from October 2017 to March 2018.

Study Site

The study was conducted in ART PLUS center of Government General Hospital, Guntur, a tertiary care teaching hospital.

Sample Size

102(n) cases(who failed first line ART)and 152 (n)controls(who had successful ART) who started ART in January-December 2012 and got failed their first line in august-2017 were taken into study.

Materials Used

Patient consent form, Pre tested standardized data collection form.

Inclusion Criteria

Age of more than 18 years, Clinic charts of HIV patients who had been initiated ART between January-December 2012 and got failed their first line in august-2017 were taken into study.

Exclusion Criteria

Clinic charts with some missing information such as treatment regimen, viral load, CD4 count and other vital information, Children and adolescent (<18yrs), Pregnant women**,** Patients who had not given consent.

Data Collection

Data was collected by reviewing the clinic chart of the patients as identified in medical records of the HIV patients to assess the factors leading failure of first line ART.

Statistical Analysis

Relative risk(RR) was used to measure the level of risk and the level of significance by chi square test for categorical data and student T test for continuous variables by using graph pad prism and SPSS version 22.00

RESULTS

FACTOR	CASES n=102	CONTROLS n=152	RR (CI-95%)	P
Age at the time of diagnosis				
20-30 yrs	32 (31.37)	43(28.8)	1.109(0.757-1.63)	0.6982
30-40 yrs	**30(29.4)**	**67 (44.07)**	**0.6673(0.470-0.95)**	**0.026***
40-50 yrs	29 (28.43)	36 (23.68)	1.2004(0.789-1.827)	0.495
>50 yrs	11(3.92)	6 (3.94)	2.7320(1.043-7.154)	0.0595
Gender				
Males	52(50.98)	83(54.6)	0.934(0.735-1.83)	0.6605
Females	50 (49.01)	69 (45.4)	1.0799(0.83-1.40)	0.6605
Marital status				
Married	67 (65.68)	107(70.39)	0.9331(0.78-1.186)	0.5130
Divorced	0(0)	10(6.57)	0.0476(0.0038-0.80)	0.0207
Single	7(6.86)	12(7.89)	0.5833(0.236-1.44)	0.9496
Widowed	**28(27.45)**	**23(8.55)**	**1.814(1.11-2.96)**	**0.0249***
Education status				
Illiterates	**67(65.68)**	**78(51.31)**	**1.280(1.04-1.58)**	**0.0324***
Primary	27(26.47)	32(21.05)	1.257(0.80-1.96)	0.3949
Secondary	**8(7.84)**	**42(27.62)**	**0.760(0.23-2.46)**	**0.0002*****

Employment				
Agricultural worker	12(11.76)	32(21.05)	0.559(0.30-1.03)	0.0804
Labour	**10(9.8)**	**35(23.02)**	**0.426(0.22-0.82)**	**0.0111***
House wives	16(15.68)	23(15.13)	1.037(0.58-1.86)	0.9043
Driver	**54(52.98)**	**52(34.21)**	**1.547(1.162-2.06)**	**0.0045****
Business	10(9.8)	10(6.57)	1.49(0.64-3.45)	0.4853
ART centre entry point				
VCTC	**98(96.07)**	**118(77.63)**	**1.24(1.127-1.36)**	**0.0001*****
Outpatient	0(0)	2(1.31)	0.297(0.014-6.12)	0.6607
Inpatient	1(0.98)	3(1.97)	0.497(0.05-4.70)	0.9130
Self referred	**1(0.98)**	**11(7.23)**	**0.135(0.018-1.03)**	**0.0453***
NGOs	0(0)	7(4.60)	0.099(0.005-1.71)	0.0708
Private	2(1.96)	4(2.63)	0.7451(0.14-3.99)	0.7300
TB RNTCP	0(0)	2(1.31)	0.301(0.014-6.2)	0.6607
PPTCT	0(0)	5(3.28)	0.135(0.007-2.41)	0.1647
Income (rupees) per month				
2000-4000	**77(75.49)**	**89(58.55)**	**1.2893(1.084-1.53)**	**0.0081****
4000-6000	**12(11.76)**	**51(33.55)**	**0.3506(0.197-0.624)**	**0.0001*****
6000-8000	**13(12.74)**	**2(1.31)**	**9.6863(2.23-42.0)**	**0.0004*****
8000-10000	**0(0)**	**10(6.57)**	**0.0707(0.004-1.19)**	**0.02***
Mode of occurrence				
Heterosexual	**53(51.96)**	**144(94.7)**	**0.55(0.45-0.663)**	**0.0001*****
Blood transfusions	1(0.98)	8(5.26)	0.1838(0.02-1.44)	0.1433
Needles	2(1.96)	0(0)	7.4272(0.3602-15.31)	0.3129
Positive family history				
Husbands	14(13.72)	24(15.7)	0.8693(0.4725-1.59)	0.785
Wives	12(11.76)	22(14.47)	0.8128(0.42-1.57)	0.6646
Children	**6(5.88)**	**1(0.65)**	**8.9412(1.09-73.1)**	**0.0355****
Type of HIV virus				
HIV 1	**64(62.74)**	**147(96.7)**	**0.6488(0.56-0.75)**	**0.0001*****
HIV 2	**36(35.29)**	**3(1.97)**	**17.882(5.66-56.52)**	**0.0001*****
Both HIV 1, 2	2(1.96)	2(1.31)	1.4902(0.21-10.41)	0.6857
WHO clinical staging at the time of initiation of ART				
Stage-1	27(26.47)	46(30.26)	0.8632(0.58-1.30)	0.6077
Stage-2	**18(17.64)**	**48(31.57)**	**0.5515(0.341-0.891)**	**0.0195***
Stage-3	48(47.05)	53(34.86)	1.3496(1.005-1.820)	0.0695
Stage-4	9(8.82)	5(3.28)	2.6821(0.9255-7.78)	0.1065
WHO present clinical staging?				
Stage-1	27(26.47)	52(34.21)	0.774(0.523-1.44)	0.2428
Stage-2	38(37.25)	74(48.68)	0.5437(0.378-0.781)	0.0950
Stage-3	28(27.45)	25(16.44)	1.669(1.0354-2.690)	0.0502
Stage-4	**9(8.82)**	**1(0.657)**	**13.41(1.725-104.2)**	**0.0032****
ART interruption				
LFUs	**10(9.8)**	**2(1.31)**	**7.45(1.67-3.33)**	**0.0047***
Wrong diagnosis of type of HIV				
	6(3.94)	**0(0)**	**19.3107(1.09-339)**	**0.0092****
Number of drug substitutions during first line ART				
Zero Substitutions	0(0)	104(68.42)	0.007(0.0004-0.113)	**0.0001*****
One Substitutions	**37(36.27)**	**29(19.07)**	**1.9013(1.254-2.88)**	**0.0035****
Two Substitutions	**23(22.54)**	**12(7.89)**	**2.856(1.49-5.48)**	**0.0017****
Three Substitutions	6(5.88)	5(3.28)	1.79(0.56-5.7)	0.4960

Four Substitutions	5(4.9)	2(1.31)	3.73(0.737-18.83)	0.1867
Type of regimen followed				
Zidovudine based	**39(38.23)**	**23(15.13)**	**2.53(1.611-3.963)**	**0.0001*** **
Stavudine based	**42(41.17)**	**21(13.9)**	**2.9804(1.881-4.720**	**0.0001*** **
Tenofovir based	**20(19.60)**	**108(71.5)**	**0.2760(0.184-0.4141)**	**0.0001*** **
Time gap between diagnosis and ART initiation				
1-6 months	**58(56.86)**	**117(76.97)**	**0.7387(1.61-0.89)**	**0.0011** **
6-12 months	**20(19.60)**	**9(5.92)**	**3.3115(1.571-6.98)**	**0.0016** **
2-6 years	7(6.86)	17(11.18)	0.613(0.263-1.42)	0.3496
>6 years	10(9.8)	9(5.92)	1.656(0.697-3.93)	0.3629
Travel time				
<60 min	**25(24.5)**	**99(65.13)**	**0.3763(0.263-0.54)**	**0.0001*** **
>60 min	**77(75.49)**	**53(34.86)**	**2.1650(1.697-2.763)**	**0.0001*** **
Drug related problems with ART drugs				
Anaemia	**45(44.11)**	**34(22.36)**	**1.972(1.365-2.85)**	**0.0004*** **
Rash	**30(29.41)**	**20(13.15)**	**2.2353(1.35-3.71)**	**0.0024** **
Peripheral neuropathy	**25(24.50)**	**12(7.89)**	**3.1046(1.635-5.89)**	**0.0005*** **
Hepatomegaly	**42(41.17)**	**3(1.97)**	**20.863(6.64-65.50)**	**0.0001*** **
Renal calculi	**20(19.6)**	**0(0)**	**60.902(3.725-995.849)**	**0.0001*** **
Opportunistic infections				
Tuberculosis	**30(29.4)**	**20(13.15)**	**2.235(1.346-3.712)**	**0.0024** **
URTI' sand LRTI's	32(31.37)	35(23.02)	1.3625(0.9056-2.0499)	0.1821
Oral candidiasis	11(10.78)	19(12.5)	0.8627(0.43-1.73)	0.8282
Diarrhoea	**14(13.72)**	**7(4.6)**	**2.980(1.25-7.13)**	**0.0185***
CMV retinitis	**9(8.82)**	**0(0)**	**28.22(1.661-479.63**	**0.0007*** **
Dermatological	**31(30.39)**	**0(0)**	**93.582(5.79-1512)**	**0.0001*** **
Number of hospitalisations				
0	88(86.27)	149(98.02)	0.880(0.812-0.954)	0.1370
1-2	**12(11.76)**	**3(1.97)**	**5.961(1.724-20.59)**	**0.0029** **
2-4	2(1.96)	0(0)	7.4272(0.36-153.12)	0.3129
Serum bilirubin levels				
<1mg/dl	**78(76.47)**	**139(91.44)**	**0.836(0.743-0.941)**	**0.0017** **
>1mg/dl	**24(23.52)**	**13(8.55)**	**2.75(1.47-5.15)**	**0.0017** **
Serum Aspartate transferase (AST)				
<34IU/L	68(66.66)	119(78.28)	0.851(0.725-1.0)	0.0554
>34IU/L	34(33.33)	43(28.28)	1.178(0.81-1.711)	0.4727
Serum Alanine transferase (ALT)				
<34IU/L	74(72.54)	121(79.60)	0.911(0.789-1.052)	0.2485
>34IU/L	28(27.45)	31(20.39)	0.911(0.789-1.05)	0.2485
Serum triglycerides and cholesterol levels				
<100mg/dl	**10(9.80)**	**62(40.78)**	**0.240(0.129-0.446)**	**0.0001*** **
100-140mg/dl	20(19.60)	39(25.65)	0.764(0.474-1.231)	0.332
140-180mg/dl	26(25.49)	39(25.65)	0.9935(0.647-1.524)	0.9760
180-220mg/dl	**12(11.76)**	**3(1.97)**	**5.846(1.691-20.209)**	**0.0029** **
>220mg/dl	**34(33.33)**	**9(5.92)**	**5.6296(2.822-11.230)**	**0.0001*** **
Random blood sugar (RBS) levels				
100-120mg/dl	62(60.78)	75(49.34)	1.232(0.9842-1.541)	0.0959
120-140mg/dl	**19(18.62)**	**77(50.65)**	**0.3677(0.238-0.568)**	**0.0001*** **
>140mg/dl	**21(20.58)**	**0(0)**	**63.8738(3.912-1042)**	**0.0001*** **
Haemoglobin				
<6gm/dl	3(2.941)	0(0)	10.3981(0.543-199.20)	0.1249

6-8g/dl	19(18.62)	18(11.84)	1.5730(0.8692-2.849)	0.1864
8-10g/dl	**37(36.27)**	**112(73.68)**	**0.4923(0.374-0.648)**	**0.0001*** **
10-12g/dl	15(14.70)	17(11.18)	1.315(0.688-2.512)	0.5246
>12g/dl	**28(27.45)**	**8(5.26)**	**5.216(2.477-10.982)**	**0.0001*** **
Adherence				
<80%	**10 (9.80)**	**1(0.657)**	**14.902(1.937-114.6)**	**0.0014** **
>90%	0 (0.00)	3(2.94)	0.212(0.011-4.065)	0.1249
>95%	**82 (80.39)**	**27(26.47)**	**4.5228(3.1726-6.45)**	**0.0001*** **
>98%	**8 (7.84)**	**112(73.68)**	**0.1064(0.0054-0.2084)**	**0.0001*** **
100%	**2(1.96)**	**9(8.82)**	**0.3312(0.073-1.501)**	**0.0001** **

CD4 COUNT

DIFFERENCE IN CD4 COUNTS BETWEEN CASES AND CONTROLS AT	ANOVA SIGNIFICANCE(P)
DIAGNOSIS	0.768
AFTER 3 YEARS ART USAGE	0.695
AFTER 6 YEARS OF ART USAGE	**0.019***

Cases had lower CD4 counts than controls after long term usage of ART that lead to treatment failure.

CORRELATION BETWEEN THE FAILURE CD4 COUNTS AND VIRAL LOAD AT TIME OF TREATMENT FAILURE IN AUGUST-2017

Correlation was done between the CD4 counts and viral load for 102 cases that started their ART between them. For these 102 cases their failure cd4 counts were taken along with their viral loads which were done in month of september-2017 and were correlated.

SAMPLE(N=)	PEARSON CORRELATION	2-TAILED SIG.
102	-0.153	0.128

CD4 and viral load were negatively correlated but not always since failure may be due to immunological failure, virological failure and due to both.

DISCUSSION

Retrospective cohort observational study was conducted to assess the factors leading to failure of first line ART and a prospective cohort observational study was conducted to assess the level of clinical progression in patient receiving second line ART. Because antiretroviral therapy (ART) restores immune function and reduces HIV-related morbidity and mortality. This advantage is eroded when virological treatment failure develops. Many patients who experience virological failure do not switch to potent second line regimens due to resource limitation, yet those who remain on a failing first-line regimen experience disproportionately higher morbidity and mortality compared to those who switch to the regimen. Several factors have been identified as predictors of treatment failure, including poor drug adherence, use of sub-optimal drug combinations, and alcohol or drug abuse and high viral load and low CD4 cell count are independently associated with mortality and changes in viral load and CD4 cell count during treatment have been associated with survival. Routine monitoring of viral load and CD4 cell counts during ART, however, indicates improved survival compared with careful clinical monitoring. The lower CD4 count likely explains the higher mortality observed in our patients and suggests second-line therapy delay increase the mortality which leads to the reduced quality of life of the patient (QOL). Hence there is a need to study the factors leading to the failure of first line anti-

retroviral therapy and clinical progression after initiation of second line ART [10].

In our retrospective study, a total of 285 clinic charts were collected from the art center who initiated their first line ART in between Jan 2012 to Dec 2012. Those subjects were grouped to cases (first line ART failure) and controls (first line ART success). 31 cases were excluded from the study due to improper data and missing information. Out of remaining 254, 152 subjects came under controls and 102 came under cases out of which 50.9% were males and 49.0% were females which was comparable to study performed by Sebunya.R et al., (2013) among 701 Ugandan children attending an urban HIV clinic" among 701 children where 45.4% were females and 54.6% were males [25].

In our study (n=254) we found that cases had more number of hospitalizations than controls, cases had low adherence levels, cases had more travel time, cases had more number of opportunistic infections, more stage-4 WHO clinical staging, and those receiving zidovudine and stavudine based regimens were associated with treatment failure which was comparable to study conducted by Sebunya.R et al.(n=701), where poor adherence to ART, a NVP based first-line regimen, prior exposure to sdNVP were associated with treatment failure [25].

In the present study(n=254) we found that there was drop of CD4 count on long term use of ART, low adherence levels, recurrent stage-3, 4 WHO clinical staging, zidovudine and stavudine based regimens, opportunistic infections , LFU's, travel time to clinic, illiteracy were associated to treatment failure which was comparable to Kwobah.CM et al.,(2012) (n=3233) among HIV-Infected African Patients where low baseline CD4 count, zidovudine-based ART and imperfect adherence were associated with first- line treatment failure [10].

In the present study (n=254) we found that 6-12 months time gap between diagnosis and ART initiation, long term use of ART lead to drop of CD4, low adherence levels, LFU's, opportunistic infections, low income levels, heterosexuality, wrong diagnosis of type of HIV virus, number of drug substitutions were the factors that lead to failure of first line ART which was comparable to Ayalew. BM et al., (n=340) among HIV patients in North West ethopia where time gap, low baseline CD4, poor adherence, LFU's, opportunistic infections were found to be significant predictors of treatment failure [33].

In our study(n=254) we found that early diagnosis, early initiation of therapy, drug adherence, heterosexuality, illiteracy, WHO clinical stage- 4 were associated with treatment failure which was comparable to Patrikar.S et al., (2015) (n=315) where late diagnoses of infection, late initiation of ART and low drug adherence were the factors which were associated with treatment failure [16].

CONCLUSION

In our study we found that controls were more among 30-40 yrs age. Males and females were equally distributed in cases and controls. Widowed females were found more among cases. Illiterates were found more among cases than controls. Cases children were more HIV seropositives than controls. Cases were more in WHO stage-4 clinical staging than controls. Cases had more number of drug substitutions, drug related adverse effects, low medication adherence, more number of LFUS and hospitalisations than controls. Cases were more in number who travels more than 60 minutes and more time gap between diagnosis and time of ART initiation and cases had raised RFTS, LFTS, and lipid profile at time of treatment failure. Cases had more serious opportunistic infections than controls.

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