Correlates of Late Presentation to HIV care in a South Indian Cohort

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Abstract. Late presentation to healthcare by HIV infected patients' is common in India despite access to free combination antiretroviral therapy (cART). We assessed risk factors for late presentation among patients with a recent HIV diagnosis in an academic university-based antiretroviral treatment center. This retrospective study included 474 recently diagnosed HIV-infected patients registered for cART between 2012 and 2013. Subjects with CD4⁺ T-lymphocyte (CD4) count $\leq$ 350 cells/ μ L or with an AIDS defining event were defined as late presenters (LP) and patients with CD4 count $\leq$ 200 cells/ μ L or with an AIDS defining event were defined as LP with advanced HIV disease (LPAD). Multivariable logistic regression analysis was used to investigate factors associated with late presentation. Of the 474 patients, 356 (75.1%) were LP. Of these, 299 (83.99%) were LPAD and 57 (16.01%) LP were AIDS-free. Median CD4 count among LP was 134 cells/ μ L (interquartile range 72.25–219). Mean age of LP was 42.50 ± 8.88 years; 256 (71.9%) were males. Increasing age (> 51 years; Adjusted odds ratio [aOR] 4.19; $P = 0.014$) and rural residence (aOR 3.19; $P < 0.001$) were independently associated with late presentation. HIV-positive housewives (aOR 0.34; $P = 0.027$), HIV-positive individuals with negative partners (aOR 0.48; $P = 0.006$), and partners with unknown HIV status (aOR 0.43; $P = 0.007$) were less likely to present late compared with positive partners of people living with HIV/AIDS (PLWHA). Most patients were LP despite free access to cART. Rural population and older PLWHA should be targeted while implementing HIV care. There is a need to strengthen the HIV care cascade by linking PLWHA to cART immediately after diagnosis.

INTRODUCTION

Late presentation to HIV care continues to be a challenge in many countries of the world including India.^{1–4} Risk factors for late presentation may vary from one setting to the other.^{2–6} Improved combination antiretroviral therapy (cART) coverage with better access to HIV care has not significantly changed the of CD4⁺ T-lymphocyte count (CD4 count) at presentation to care.^{7,8} Because of immunosuppression, these late presenters (LP) have an increased rate of opportunistic infection (OI), AIDS and death.^{3,9,10} This increase in morbidity and mortality associated with late presentation significantly enhances the cost of therapy.¹¹ High viral load associated with late presentation increases the transmission risk of HIV in the community.^{12,13} Advanced disease with marked immunosuppression may result in suboptimal immune recovery after initiation of cART.¹⁴

Late presentation to HIV care has an adverse impact on the outcome of cART programs.¹⁵ Recent estimates indicate that 30–50% still present late to HIV care.¹ In India, at the end of 2016, there were about 2.1 million PLWHA, of which 49% were on cART.¹⁶ Since 2004, free cART is available in India as part of the national antiretroviral treatment (ART) program, but many PLWHA continue to present late to HIV care.^{4,17}

Periodic data analysis from ART centers is important to address gaps in the HIV care continuum to improve effectiveness of the ART program. Various methods and designs have been used to study the HIV care cascade and define correlates of late presentation to HIV care.^{5,18} We have used a cross-sectional design using a chart review method to analyze

correlates of LP. The objectives of our study were to quantify proportion of PLWHA presenting late for treatment in a South Indian cohort and to evaluate potential factors associated with late presentation to cART.

MATERIALS AND METHODS

Design and setting. This retrospective study was performed between February 2012 and February 2013 at the Kasturba Medical College Hospital, a 750-bed tertiary care referral teaching hospital situated in Mangalore, a coastal city in the Dakshina Kannada (DK) district of the southern state of Karnataka, India. Mangalore city has a population of 4.9 lakhs, and HIV prevalence in the DK district is estimated at 0.50%.^{19,20}

Patients. During the study period, as per the National AIDS Control Organization of India (NACO) guidelines, initial evaluation for subjects diagnosed with HIV included measurement of CD4 count and screening for OI followed by initiation of cART for all eligible PLWHA if their CD4 count was of $\leq$ 350 cell/ μ L or they were in WHO stage III or stage IV. The study population included a cross-sectional sample of HIV antiretroviral naïve patients aged ≥ 18 years enrolled for first line cART. Patients diagnosed to be HIV-positive > 1 year before the initiation of cART and with history of AIDS defining conditions before 6 months of initiation of cART were excluded from analysis. There were two subsets of study participants: 1) Those referred with an illness for voluntary counseling and testing for HIV; and 2) subjects who were diagnosed to have HIV infection within the previous year being referred for cART. We excluded patients diagnosed to be HIV-positive but not initiated on cART. They were either not eligible for treatment as per NACO guidelines or they did not wish to be treated. All enrolled subjects had received non-nucleoside reverse transcriptase inhibitor-based cART.

Data collection. Data were collected using a semi-structured case report form template similar to the one used in NACO ART centers. Sociodemographic characteristics

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(e.g., age, gender, education level, residence, socioeconomic status, alcohol use, partners' self-reported HIV status, and route of sexual exposure), CD4 count, OIs, AIDS defining events, and WHO stage at the time of presentation to HIV care for initiation of cART were collected. Area of residence was categorized as per the national census 2011 definitions.¹⁹ Alcohol use was considered significant if the drinking pattern involved daily consumption of up to two drinks in males and up to one drink in females (United States Department of Health and Human Services and United States Department of Agriculture dietary guidelines, 2015–2020).

Definitions. Patients presenting to HIV care with a CD4 count ≤ 350 cell/ μ L or with an AIDS defining event regardless of CD4 count were defined as LP based on European LP Consensus definition. Those subjects presenting to HIV care with a CD4 count ≤ 200 cell/ μ L or with an AIDS defining event regardless of CD4 count were defined as late presentation with advanced HIV disease (LPAD).²¹

Statistical analysis. Statistical analyses were performed by grouping the patients as LP and non-late presenters (nLP). Subgroup analysis was performed by categorizing LP into LPAD and LP but AIDS free (LPAF). Descriptive statistics were calculated as mean (SD) for variables that were normally distributed and as median (IQR) for variables influenced by extreme values.

Comparison was carried out among LP and nLP for socio-demographic factors such as age, gender, area of residence, occupation, monthly income, educational status, sexual behavior, alcohol use, and self-reported HIV status of spouse, to analyze for possible association with late presentation. Association between categorical variables and late presentation was analyzed using chi-square test or Fisher's exact test. Comparison of mean income and CD4 count were performed by independent sample *t*-test. Median CD4 count in LP/nLP and LPAD/LPAF groups were compared by using Mann-Whitney *U* test.

Variables found to be statistically significant by Univariate/Bivariate analysis were subjected to multivariable analysis using binary logistic regression to predict the independent factors responsible for late presentation. A *P* value < 0.05 was considered statistically significant. Data were analyzed using SPSS Version 24 (IBM Corp, Armonk, NY).

RESULTS

Between February 2012 and February 2013, 474 treatment-naïve HIV patients were enrolled for cART. Of 474, 327 (69%) were males. The mean age of the study population was 41.60 ± 9.28 years; 78 (16.5%) were aged > 50 years. Of the cohort, 469 (98.9%) reported their HIV exposure category as heterosexual. The majority of participants lived in rural areas 342 (72.2%). Of the 474 new HIV diagnoses, 356 (75.1%) were LP; of these, 299 (83.99%) had LPAD and 57 (16.1%) were LPAF. Median CD4 count was 188.5 cells/ μ L (IQR 93.75–366.25). Median CD4 count among LP was 134 cells/ μ L (IQR 72.25–219) (Table 1).

Of the 474 patients analyzed, 238 (50.2%) had no OI. Tuberculosis (TB) was the major OI among LP and nLP. Thirty-two (6.8%) had pulmonary TB, 103 (21.7%) had extrapulmonary TB at initiation of cART, whereas 101 (21.3%) had other AIDS defining conditions (cerebral Toxoplasmosis, Cytomegalovirus retinitis, Cryptococcal meningitis, and *Pneumocystis jirovecii* pneumonia) (Table 1).

Risk factors for late presentation to cART. Univariate/Bivariate analysis showed a significant statistical association between LP and age ($P = 0.010$), gender ($P = 0.021$), residence ($P < 0.001$), occupation ($P = 0.002$), and HIV status of spouse ($P = 0.003$). Multivariate analysis predicted age (26–50 years, aOR 2.94, $P = 0.036$; and ≥ 50 years, aOR 4.19, $P = 0.014$) and rural residence (aOR 3.19, $P < 0.001$) as independent risk factors for LP. HIV-positive housewives (aOR 0.34, $P = 0.027$), HIV-positive individual with a negative partner (aOR 0.48, $P = 0.006$), and partners with unknown HIV status (aOR 0.43, $P = 0.007$) were less likely to present late for HIV care (Table 2).

DISCUSSION

Despite the availability of free cART in our setting, 75.1% were found to be LP, of whom 83.9% were LPAD at the time of their referral to cART. Our findings are consistent with other reports from other states in India.^{4,22} Late presentation with low baseline CD4 counts is the strongest prognostic marker for early mortality in high-, low-, and middle-income countries.^{7,8} In one study from New Delhi involving 2,936 subjects, 83.37% were LP.⁴ In another report from the state of Andhra Pradesh, 68.7% of patients were LP and 46% were LPAD.²²

Studies indicate that males were more likely to present late as compared with females.^{4,23} We found an association between gender and late presentation to cART by Univariate/Bivariate analysis. However, on multivariable analysis when gender was adjusted with other independent factors, gender was not found to be a risk factor for late presentation. Females are routinely tested for HIV infection during prenatal or pregnancy screening, and therefore have an enhanced chance of early diagnosis and initiation of cART.

In our HIV cohort, patients aged > 50 years were more likely to present late compared with patients aged < 25 years. Late diagnosis with late entry into HIV care was the main reason for this observation in our cohort. The association of late presentation with older age has been well described and may be related to many factors (e.g., low self-perceived risk, high-risk behaviors, and missed opportunities in clinical settings). Older PLWHA have a higher risk of mortality and a lower CD4 count at diagnosis.^{24–26}

The risk of mortality is significantly high in PLWHA in rural areas due coinfections.²⁷ In our study cohort, PLWHA in rural areas were almost three-times more likely to present late for care. This could be because of the lack of access to quality health care in rural areas and long travel distance to reach urban health centers. Rural areas were situated at about 25–35 km from the urban ART centers, and PLWHAs from rural areas were mainly daily wage earners involved in farming and small business. Travel from village, resulting in loss of wages, is a barrier to access health care in cities in earlier studies.

Occupation categorized as salaried job, daily wage earners, business, and housewives was also associated with late presentation. Housewives are considered vulnerable to acquire HIV in India.^{28,29} Men working in urban metropolitan cities acquire infection first only to transmit it to their wives later when they return home, situated in villages. But housewives with HIV-positive status were less likely to present late to care compared with PLWHA with a salaried job. This could be because of a better social support emerging out of the responsibility on the young housewife in managing the home when their husbands are out working in cities and providing

TABLE 1
Patient characteristics at the time of initiation of cART in LP and nLP

Variables	Total, N = 474 (100%) n (%)	Late presenters, N = 356 (75.1%) n (%)	Non-late presenters, N = 118 (24.9%) n (%)	P value
Age in years				0.010
≤ 25	19 (4%)	9 (2.5%)	10 (8.5%)	
26–50	377 (79.5%)	284 (79.8%)	93 (78.8%)	–
≥ 51	78 (16.5%)	63 (17.7%)	15 (12.7%)	–
Mean age in years*	41.60 (±9.28)	42.5 (±8.88)	38.86 (±9.93)	< 0.001
Median age in years†	41 (IQR 35–47)	42 (IQR 37–47.75)	38 (IQR 32–46)	< 0.001
CD4 T-cell count				
Mean CD4 T-cell count*	253.63 (±210.730)	155.46 (±103.06)	549.83 (±171.73)	< 0.001
Cells/μL*	–	–	–	–
Median CD4 T-cell count	188.50 (IQR 93.75–366.25)	134 (IQR 72.25–219)	515 (409.50–627.25)	< 0.001
Cells/μL†	–	–	–	–
Gender				0.021
Female	147 (31%)	100 (28.1%)	47 (39.8%)	
Male	327 (69%)	256 (71.9%)	71 (60.2%)	
Residence				< 0.001
Urban	132 (27.8%)	79 (22.2%)	53 (44.9%)	
Rural	342 (72.2%)	277 (77.8%)	65 (55.1%)	
Economic status: income/month in INR				0.577
≤ 2,000	80 (16.9%)	63 (17.7%)	17 (14.4%)	
2,001–5,000	279 (58.9%)	210 (59%)	69 (58.5%)	–
≥ 5,001	115 (24.2%)	83 (23.3%)	32 (27.1%)	
Mean income in INR*	4,631.66 (±3,559.16)	4,432.25 (±2,901.44)	5,233.26 (±5,103.94)	0.036
Education				0.863
Nonliterate	31 (6.5%)	22 (6.2%)	9 (7.6%)	
Primary	231 (48.8%)	172 (48.3%)	59 (50%)	
Secondary	158 (33.3%)	122 (34.3%)	36 (30.5%)	
College	54 (11.4%)	40 (11.2%)	14 (11.9%)	
Occupation				0.002
Salaried	51 (10.8%)	39 (11%)	12 (10.2%)	
Daily wage earners	282 (59.5%)	213 (59.8%)	69 (58.5%)	
Business	55 (11.6%)	50 (14%)	5 (4.2%)	
Housewife	86 (18.1%)	54 (15.2%)	32 (27.1%)	
HIV status of spouse				0.003
Negative	134 (28.3%)	90 (25.3%)	44 (37.3%)	
Positive	264 (55.7%)	214 (60.1%)	50 (42.4%)	
Unknown	76 (16%)	52 (14.6%)	24 (20.3%)	
Marital status				0.839
Single/unmarried	54 (11.4%)	41 (11.5%)	13 (11%)	
Married	387 (81.6%)	292 (82%)	95 (82.5%)	
Divorced	12 (2.6%)	9 (2.5%)	3 (2.5%)	
Widow/widower	21 (4.4%)	14 (4%)	7 (5.9%)	
Exposure route				1.00
Homosexual	5 (1.1%)	4 (1.1%)	1 (0.8%)	
Heterosexual	469 (98.9%)	352 (98.9%)	117 (99.2%)	
Alcohol use				0.59
Yes	199 (42%)	152 (42.7%)	47 (39.8%)	
No	275 (58%)	204 (57.3%)	71 (60.2%)	
WHO stage				< 0.001
Stage I	102 (21.5%)	30 (8.4%)	72 (61%)	
Stage II	53 (11.2%)	19 (5.3%)	34 (28.8%)	
Stage III	111 (23.4%)	99 (27.8%)	12 (10.2%)	
Stage IV	208 (43.9%)	208 (58.5%)	0 (0%)	
OIs				< 0.001
No OI	238 (50.2%)	122 (34.3%)	116 (98.3%)	
Pulmonary TB	32 (6.8%)	30 (8.4%)	2 (1.7%)	
Extra pulmonary TB	103 (21.7%)	103 (28.9%)	0 (0%)	
Other AIDS defining conditions	101 (21.3%)	101 (28.4%)	0 (0%)	

cART = combination antiretroviral therapy; LP = late presenters; nLP = non-late presenters; OI = opportunistic infection.

* Independent sample t-test.

† Mann-Whitney U test.

financial support. In addition, ease of getting registered at the same ART center as their spouse also reduces the difficulty involved in accessing the treatment. During prenatal/pregnancy, they are encouraged to undergo HIV testing further enhancing their chance of timely diagnosis and treatment.

Self-reported HIV status of the spouse had a significant association with late presentation. Compared with PLWHA

with positive partners, those with negative partners in a discordant relationship or partners with unknown HIV status were less likely to present late for treatment. This health-seeking behavior could be because of concern for the partner who is either HIV negative or with unknown HIV status.

Studies have identified intravenous drug use (IDU), unemployment, being heterosexual, and homelessness as risk

TABLE 2
Independent predictors of late presentation to cART

Variable	Total, N = 474 (100%) n (%)	Adjusted odds ratio	Odds ratio 95% CI	P value
Age in years				
≤ 25	19 (4%)	1		
26–50	377 (79.5%)	2.94	1.08–8.02	0.036
≥ 51	78 (16.5%)	4.19	1.33–13.15	0.014
Gender				
Female	147 (31%)	1		
Male	327 (69%)	1.12	0.56–2.22	0.758
Residence				
Urban	132 (27.8%)	1		
Rural	342 (72.2%)	3.19	1.98–5.13	< 0.001
Occupation				
Salaried	51 (10.8%)	1		
Daily wage earners	282 (59.5%)	0.65	0.30–1.41	0.278
Business	55 (11.6%)	2.30	0.71–7.45	0.165
Housewife	86 (18.1%)	0.34	0.13–0.89	0.027
HIV status of spouse				
Positive	134 (28.3%)	1		
Negative	264 (55.7%)	0.48	0.29–0.81	0.006
Unknown	76 (16%)	0.43	0.23–0.79	0.007

cART = combination antiretroviral therapy; CI = confidence interval.

factors for late presentation.^{4,15} We did not have participants who reported IDU in our study. Educational level had no significant association with late presentation. However, subgroup analysis of LP as LPAD and LPAF indicated an association of education level with LPAD. Health literacy level, enabling patients to comprehend and process the health-related information, could be a better indicator,^{30,31} but we did not investigate it.

In India, there is no recommendation for routine HIV testing of adults and adolescents.³² HIV treatment cascade has significant dropout at every step from HIV diagnosis, linkage to care, retention in care, and in attaining virological suppression.^{16,17} Patients are often diagnosed late with late entry into HIV care.³³ Delay in initiation of cART after diagnosis is known to be associated with patients being lost to follow-up with delayed presentation for treatment at a later date.^{33,34} We analyzed patient data at the initiation of cART and not at entry into HIV care at diagnosis. In May 2017, NACO implemented a change in HIV treatment guideline to treat all individuals with HIV irrespective of CD4 count.³⁵ A treat-all policy could reduce pre-cART waiting period and dropout rates because of difficulty in maintaining linkage to care while the CD4 count goes down, thereby reducing the risk of late presentation.³⁶ Our study highlights the risk of initiation of cART based only on CD4 count cut-off values.

Our study had several limitations including retrospective chart review, inclusion of a single urban academic hospital site with possible selection bias and reduced generalizability. We might have overestimated the proportion of LP because subjects diagnosed with HIV but not initiated on cART were excluded if they had a CD4 count > 350 cells/μL and were in WHO stage I or stage II. Despite these limitations, our data provide considerable insight to program managers and policy makers to improve HIV care at both the local and national levels for individuals with a new diagnosis of HIV infection.

CONCLUSION

Most patients were LP despite free access to cART. Rural population and older PLWHA should be targeted while

implementing HIV care. HIV care programs in India must aim at strengthening the HIV-care cascade by linking PLWHA to cART immediately after HIV diagnosis.

Received May 4, 2018. Accepted for publication August 6, 2018.

Published online September 17, 2018.

Acknowledgments: We thank Dr. John T. Ramapuram, TMA Pai endowment chair, HIV and opportunistic infections, Manipal Academy of Higher Education, India for his support.

Conflicts of interest: All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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