

# Determinants of rapid progression to immunodeficiency syndrome among people infected with Human Immunodeficiency Virus, Kerala, India

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## Abstract

**Context:** Human Immunodeficiency Virus (HIV) infection progresses in almost all infected persons to Acquired Immunodeficiency Syndrome (AIDS). The aim of the study was to find out the determinants of rapid progression of immunodeficiency among people infected with HIV in Thiruvananthapuram district of Kerala, India. **Settings and Design:** The study design used was case control. The setting of the study was antiretroviral treatment (ART) centre of Government Medical College and the self-help group of HIV patients located at Thiruvananthapuram, Kerala. **Materials and Methods:** Cases were people having any one or more of the AIDS defining clinical conditions within 3 years from the diagnosis of HIV infection. Controls were people diagnosed as having HIV at least 3 years ago and with no AIDS-defining clinical conditions till the date of the study. Sample size was 149 with a control case ratio of 1.5:1. **Statistical analysis used:** Mean (standard deviation) and proportions were used to describe the data. Chi-square test and t test were done to test the hypotheses. Binary logistic technique was used to find out the predictors of the outcome. **Results:** A regression (Binary Logistic) model was used to predict the progression. Fungal infection of nail [adjusted Odds Ratio (OR), 6.4 (1.4, 28.9)] and oral candidiasis [adjusted OR, 2.6 (1.1, 6.4)] were the clinical conditions significantly associated with rapid progression. The significant social factors included non-exposure to professional counseling [adjusted OR, 7.1 (2.0, 24.5)] and the feeling of being stigmatized - felt as preoccupation with thoughts that they are gossiped about and the increase in visitors to “check them out” [adjusted OR, 26.1 (4.9, 138.4)]. The protective nutritional factors in the model were frequent consumption of legumes [adjusted OR, 0.12 (0.04, 0.36)], eggs [adjusted OR, 0.29 (0.09, 0.93)], and plenty of oral fluids [adjusted OR, 0.18 (0.07, 0.47)]. **Conclusions:** An approach incorporating the clinical, social, and nutritional factors may retard the progression of HIV infection.

**Key words:** Determinants of progression, HIV in Kerala, HIV in India, progression of HIV infection, progression of immunodeficiency, risk factors of progression

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## INTRODUCTION

Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) has become one of the leading causes of mortality among adults aged 15–59 years contributing to about 14% of deaths globally in this age group.<sup>[1]</sup> HIV infection progresses in almost all infected persons from a clinically silent

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stage to a severely damaged immunologic function resulting in AIDS. The progression of infection is very slow in the post antiretroviral (ART) era and the death rates are comparable with that of the normal population.<sup>[2]</sup> Highly variable disease progression rates between individuals are well recognized, with progression categorized as rapid, typical, intermediate, and late or long-term non-progression.<sup>[3]</sup>

The progression of clinical syndrome in HIV/AIDS may depend upon various factors. A significant association of CD4 counts with the bad outcome is identified in some researches.<sup>[4]</sup> A high viral load which does not fall dramatically after primary HIV infection is related to rapid progression. Some rapid progressors may be infected with more rapidly replicating, virulent HIV strains.<sup>[5]</sup> The risk of AIDS almost always correlates with the reduction in CD4 count and the CD4+ T-cell count is the most significant predictor of disease progression and survival.<sup>[6]</sup>

The studies on the bio molecules related to immune activation such as neopterin,<sup>[7,8]</sup> tumor necrosis factor type II receptor,<sup>[7]</sup>  $\beta_2$ -microglobulin,<sup>[9]</sup> endogenous interferon,<sup>[8]</sup> and tumor necrosis factor- $\alpha$ <sup>[10]</sup> give conflicting results. A few studies describe the role of modifiable entities like nutritional factors, body mass index (BMI),<sup>[11]</sup> and blood level of Vitamin A.<sup>[12]</sup> Social factors like social support, stressful life events, depression, and denial-based coping strategies<sup>[13]</sup> were addressed in a few occasions.

The aim of the study was to find out the determinants of rapid progression to immunodeficiency among people infected with HIV in Thiruvananthapuram district of Kerala, India.

## MATERIALS AND METHODS

The study design used was case control. Cases were 'Rapid Progressors' defined as people infected with HIV with the occurrence of any one or more of the adverse outcomes listed below within 3 years from the diagnosis of HIV infection. Controls were people infected with HIV diagnosed at least 3 years ago without any of the adverse outcomes listed below. The adverse outcomes were Kaposi's sarcoma, Lymphoma, Pneumocystis carinii pneumonia, Toxoplasmosis, Esophageal candidiasis, Cryptococcosis, Cryptosporidiosis, recurrent Herpes simplex infection, Tuberculosis, Cytomegalovirus retinitis, cerebral lymphoma, and *Mycobacterium avium* complex infection (MAC).

The subjects under this study were selected from two settings. One was the self-help group of HIV patients in the district known as Prathyasha centre, which is a part of the Indian Network of People with HIV/AIDS (INP) and the other was the clinic for ART in Medical College Hospital, Thiruvananthapuram. ART centre is a place where all the HIV infected individuals are registered soon after their infection status is revealed. The patients visit ART clinic further for anti retroviral chemotherapy to test their CD4 count or as advised by the physician after the development of some health problems. So it is highly likely that the proportion of cases may be high in this setting. On the other hand, the self-help groups of HIV-infected people represent a community setting where relatively healthy (HIV infected) people assemble. We included both the community setting and clinic to ensure adequate numbers in both the study groups.

The study subjects were adults, with age more than or equal to 18 years. The laboratory report of the patients indicating their HIV status, the latest CD4 count report, and medical history were verified before enrolling them into the study. All the prevalent cases fulfilling the eligibility criteria were included in the study as cases and all the consecutive patients as per the criteria for non-rapid progressors given above were enrolled as controls. The CD4 count testing is done for every HIV infected person at the time of detection of their HIV positivity. Those who became aware of their infection status for duration of less than 36 months and have not developed any of the AIDS defining clinical conditions till the date of interview were excluded from the study. Five subjects were excluded as they were unwilling to participate in the study. The study period was from 15<sup>th</sup> November to 30<sup>th</sup> December 2008. The total sample size was 149 with 89 controls and 60 cases with a control: case ratio of 1.5:1.

Sociodemographic variables like age, sex, education, and occupation; anthropometric variables like BMI; CD4 count at the time of knowledge of infection; social support mechanisms ;opportunistic infections and hospitalizations; stigma; cop-up skills; health seeking behavior; feeding habits; sleep; recreational activities; co-morbidities like diabetes and hypertension were measured as co-variables. The association of co-variables to the outcome variable, progression of HIV infection to AIDS was measured using bivariate analysis and multivariate techniques.

The study tool was a structured interview schedule developed with the help of experts from

the Infectious Disease department of Medical College Hospital, Thiruvananthapuram. The tool was validated qualitatively with the help of methodologists in the department of Community Medicine, Medical College, Thiruvananthapuram and the Clinical Epidemiology unit of the Medical College. The tool was piloted at Prathyasha clinic. The USAID questionnaire <sup>[14]</sup> was translated and validated to measure the community level stigma.

### Statistical analysis

The quantitative variables under study were described by mean with its 95% confidence intervals and qualitative variables with frequencies and proportions. The statistical significance of the associations was tested using independent sample t test if the distribution under study was quantitative. Chi-square test was used in case of qualitative variables. Binary logistic regression was used to find out independent predictors of the outcome. The Odd's ratio with its confidence interval given by the model was used to assess the strength of association in the final analysis.

### Ethical approval

The clearance from the institutional ethical committee was obtained before the commencement of the study. Written informed consent was obtained from all the study subjects. Privacy and confidentiality of the study subjects was maintained during all stages of the study.

## RESULTS

The analysis included the data of 149 subjects of which 59 were collected from the self-help group of HIV patients and 90 from ART clinic. Sixty patients fulfilled the case definition of rapid progressors. Although twelve AIDS defining conditions were included in the case definition, in our study three of them determined all the cases. Fifty one (85%) had tuberculosis, sixteen (26.7%) had Esophageal candidiasis, and fifteen (25%) had Pneumocystis carinii pneumonia. The control group consisted of 89 people who fulfilled the case definition of slow progressors. Most of these people (83.1%) have not been affected by any AIDS defining disease till the date of survey. But fifteen (16.9%) have an experience of tuberculosis but only after at least 3 years of the knowledge of their infection status. More than 90% of people in the case group were on ART, while only 64% in the control group were on ART [Table 1].

The mean age of the rapid progressors, 41.37 years (39.73–43.01) was significantly higher than that of

the controls, 38.67 years (37.17–40.17) [Table 1]. A male predominance was seen in the case group [Table 1]. More than 90% of people in both the arm were married [Table 1] and there was no rural-urban difference noted. The difference in education was not statistically significant [Table 1]. More than 40% of people in the case group were dependent on others for their daily living [Table 1].

Hetero sexual route was the most common route (73.3% of cases and 79.8% of controls) of infection. Homosexuals were not identified. The two groups differed significantly in terms of initial CD4 count. The initial mean CD4 count was  $217 \times 10^6/L$  in the case group where as it was  $309 \times 10^6/L$  in the control group.

As is evident from Table 1, the mean BMI of the case group, 17.9 (17.0–18.8) was just touching the lower range of biological normal limits. Almost 50% of people in this group were malnourished, whereas in the control group the mean BMI was 21.1 (20.3–21.9). The two groups under study did not differ significantly in their duration of sleep. The mean duration of sleep was 7.03 (6.65–7.41) hours in the case group and 7.36 (7.02–7.70) hours in the control group. But people having a habit of listening to music and reading books [Table 2] were at a lower risk when disease progression was considered. But other hobbies were not found influencing the disease progression significantly. Health seeking was more in the control group but within the range of chance variation. Food material taken at least one serving per week was asked and the variables were categorized using the median number of servings. Significantly larger proportion of non-rapid progressors consumed protein rich food materials like legumes and egg [Table 2]. The consumption of protective food materials like green leafy vegetables was also more in case of the non-rapid progressors. The mean daily intake of water was found slightly higher in the control group (1720 ml/day) than in the case group (1440 ml/day).

Table 2 shows that three factors under social support mechanisms namely receiving counseling/emotional support from a social worker who was trained under National AIDS Control Program (ICTC counseling), availability of a friend to help and involvement in some social organizations significantly reduced the progression to AIDS. Community level stigma was assessed using the USAID questionnaire [Table 2]. Seventeen people from the case group (28.3%) and twenty from the control (22.5%) group had to shift their residence at least once after the recognition of their infection status. The mean stigma score among

rapid progressors was 2.28 (1.48–3.08) and that of non-rapid progressors was 1.48 (1.05–1.91). The cases were different significantly from the controls in two factors. They think they are frequently gossiped about and also that visitors increase to “check them out.” [Table 2]

The rapid progressors had experienced significantly more episodes of oral candidiasis, skin infections, fungal infection of the nail, bacterial pneumonia, and unintentional weight loss more than 10% of the original weight and diarrhea lasting for more than two weeks during their travel from HIV infection to AIDS [Table 2]. The difference between the two groups was not marked in case of recurrent attacks of Chicken pox or Zoster, Seborrhoeic dermatitis, and genital candidiasis [Table 2].

Prediction of progression within 3 years of diagnosis of HIV was tried using multivariate analysis (Binary logistic regression) [Table 3]. Those who did not get counseling from ICTC, patients who felt that visitors increased to “check them out”, those experiencing fungal infections of nail or oral candidiasis were at a higher risk. Consumption of legumes, consumption of eggs, and frequent oral fluids may offer protection.

## DISCUSSION

In this study, cases were found to be significantly older [Table 1]. It is also noted elsewhere that mortality and AIDS incidence increased strongly with age at seroconversion.<sup>[15]</sup> It is not clear what made older people more vulnerable to rapid progression but may be because of delayed recognition of older individuals with occult HIV disease.<sup>[16]</sup> Some authors argue that older people

suffer from more severe depletion of CD4+ compared to their younger counter parts.<sup>[17]</sup> This finding is contradictory to that of the US Navy report which observes that the rapid progressors have a slightly younger age than slow progressors.<sup>[18]</sup>

The difference of the study groups in gender should be viewed in the background of potential confounding. In a family, man may usually be contracting the infection first. It may take years for his spouse to get infected. Both the members of the family will be aware of the infection only when the male counter part suffers from some opportunistic infections. But another study from south India also shows a similar finding that HIV infected men progress at a faster rate compared to women.<sup>[19]</sup>

The mean value of CD4 count at the time of knowledge of the infection status is significantly higher in slow progressors. Studies in this regard all over the world demonstrate that low CD4+ is one of the most significant predictors of progression in HIV/AIDS along with the plasma viral load.<sup>[20,21]</sup>

A few studies have addressed the relationship between nutritional status indicators like serum vitamin A levels and HIV disease progression.<sup>[12]</sup> Lower serum retinol levels were observed in Rapid Progressors.<sup>[12]</sup> The current study also argues that protein rich food offer some protection against the progression of HIV infection. The case group is significantly different from the control group in terms of initial BMI (BMI at the time of knowledge of their infection) [Table 1]. Malnutrition in HIV infected patients can hasten the progression of the disease process and at the same time the infection and other risk factors can make the patients more

**Table 1: Comparison of cases and controls**

Qualitative variables			
Factor	Rapid progressor N (%)	Non-rapid progressor N (%)	P value (chi-square)
ART taken	55 (91.7)	57 (64)	0.000
Women	22 (36.7)	50 (56.2)	0.019
Education secondary level or more	47 (78.3)	57 (64)	0.062
Residence in a rural area	50 (83.3)	76 (85.4)	0.733
Married	56 (93.3)	86 (96.6)	0.351
Dependent on others	25 (41.7)	25 (28)	0.085
Hetero sexual route	44 (73.3)	71 (79.8)	0.358
Quantitative variables			
Factor	Rapid progressor Mean (95% CI)	Non-rapid progressor Mean (95% CI)	P value (t test)
Initial CD4 count in 106/L	217 (175-259)	309 (267-351)	0.004
Initial BMI	17.9 (17.0-18.8)	21.1 (20.3-21.9)	0.000
Time of start of ART (months)	8.83 (3.33-14.03)	30.32 (19.12-41.42)	0.001

**Table 2: Bivariate analysis of exposure factors**

Factor	Rapid progressor N (%)	Non-rapid progressor N (%)	Odds ratio (95% CI)	P value (chi-square)
Social support system				
Received counseling/emotional support from a medical doctor	43 (71.7)	61 (68.5)	1.16 (0.53-2.54)	0.683
Received counseling/emotional support from a person who is trained in giving counseling for HIV patients (ICTC or VCTC counseling*)	44 (73.3)	79 (88.8)	0.35 (0.13-0.90)	0.015
Availability of someone as a 'friend in need'	22 (36.7)	54 (60.7)	0.38 (0.18-0.78)	0.004
Support from a psychiatrist	9 (15)	15 (16.9)	0.87 (0.32-2.32)	0.763
Help of family members other than spouse	26 (43.3)	50 (56.2)	0.60 (0.29-1.22)	0.124
Economic help from outside the family	12 (20)	22 (24.7)	0.76 (0.32-1.80)	0.501
Participation in social activities as a member of social organizations	35 (58.3)	66 (74.2)	0.49 (0.23-1.04)	0.043
Personal attributes (as perceived by the respondent)				
Having a habit of listening to music	34 (56.7)	68 (76.4)	0.40 (0.19-0.87)	0.011
Having reading books as a hobby	17 (29.3)	45 (51.7)	0.39 (0.18-0.82)	0.005
Having any other hobbies	17 (28.8)	32 (36.0)	0.70 (0.33-1.51)	0.366
Medical seeking even for mild ailments	31 (51.7)	55 (61.8)	0.62 (0.30-1.28)	0.220
Stigma**				
Excluded from a social gathering.	19 (31.7)	17 (19.1)	1.9 (0.86-4.49)	0.079
Lost customers to buy his/her produce/goods or lost a job.	6 (10)	16 (18)	0.51 (0.16-1.50)	0.178
Had property taken away.	5 (8.3)	13 (14.6)	0.53 (0.15-1.73)	0.249
Abandoned by spouse/partner.	7 (11.7)	3 (3.4)	3.8 (0.83-19.4)	0.090
Teased or sworn at.	14 (23.3)	13 (14.6)	1.8 (0.71-4.46)	0.175
Abandoned by family/sent away to the village.	6 (10)	6 (6.7)	1.5 (0.74-5.74)	0.546
Lost respect/standing within the family and/or community.	12 (20)	12 (13.5)	1.6 (0.61-4.20)	0.289
Gossiped about.	22 (36.7)	19 (21.3)	2.1 (0.97-4.72)	0.040
No longer visited, or visited less frequently by family and friends.	13 (21.7)	15 (16.9)	1.4 (0.55-3.37)	0.461
Visitors increase to "check them out,"	17 (28.3)	5 (5.6)	6.6 (2.11-22.2)	0.000
Isolated within the household.	16 (26.7)	13 (14.6)	2.1 (0.87-5.23)	0.068
History of opportunistic infections***				
Second attack of Chickenpox or Zoster	5 (8.3)	14 (15.7)	0.49 (0.14-1.57)	0.183
Oral candidiasis	41 (68.3)	35 (39.3)	3.33 (1.59-7.06)	0.001
Skin infections needed medical care	25 (41.7)	22 (24.7)	2.18 (1.02-4.68)	0.029
Seborrheic dermatitis	13 (21.7)	12 (13.5)	1.77 (0.69-4.58)	0.190
Fungal infection nail	15 (25.0)	4 (4.5)	7.08 (2.03-27.03)	0.000
Bacterial pneumonia	17 (28.3)	10 (11.2)	3.12 (1.22-8.12)	0.008
Unintentional weight lose >10%	24 (40.0)	15 (16.9)	3.29 (1.45-7.54)	0.002
Diarrhea lasting for more than two weeks	13 (21.7)	7 (7.9)	3.24 (1.11-9.75)	0.015
Genital candidiasis	13 (21.7)	24 (27.0)	0.75 (0.32-1.73)	0.463
Food habits****				
Wheat	24 (40.0)	44 (49.4)	0.68 (0.33-1.39)	0.257
Legumes	13 (21.7)	48 (53.9)	0.24 (0.10-0.53)	0.000
Milk	48 (80.0)	69 (77.5)	1.16 (0.48-2.8)	0.719
Fish	54 (90.0)	82 (92.1)	0.77 (0.22-2.76)	0.651
Poultry	3 (5.0)	6 (6.7)	0.73 (0.14-3.46)	0.662
Beef or mutton	3 (5.0)	5 (5.6)	0.88 (0.16-4.48)	0.870

Table 2 (contd...)



**Table 2: contd...**

Factor	Rapid progressor N (%)	Non-rapid progressor N (%)	Odds ratio (95% CI)	P value (chi-square)
Green leafy vegetables	38 (63.3)	75 (84.3)	0.32 (0.14-0.75)	0.003
Fruits	28 (46.7)	43 (48.3)	1.14 (0.57-2.28)	0.843
Eggs	9 (15)	28 (31.5)	0.38 (0.15-0.95)	0.023
Snacks	12 (20)	18 (20.2)	0.99 (0.40-2.40)	0.973
Supplementary foods	6 (10)	16 (18.0)	0.51 (0.16-1.50)	0.178

\*Voluntary Counseling and Testing Centre (VCTC) under National AIDS Control Program of India. Renamed as Integrated Counseling and Testing Centre (ICTC) in 2008, \*\*As perceived by the respondent, \*\*\*Other than the AIDS defining diseases used to categorize the patients as case and control, \*\*\*\*At least 3 servings per week as perceived by the respondent. The quantity of the units of servings is not calculated.

**Table 3: Multivariate analysis of exposure factors**

Factor	Adjusted OR with 95% CI	P value
Patients did not get counseling from VCTC	7.1 (2.0-24.5)	0.002
Patients feel that Visitors increase to "check them out."	26.1 (4.9-138.4)	0.000
Fungal infection of nail	6.4 (1.4-28.9)	0.015
Candidiasis- oral	2.6 (1.1-6.4)	0.035
Consumption of legumes	0.12 (0.04-0.36)	0.000
Consumption of eggs	0.29 (0.09-0.93)	0.037
Water consumption	0.18 (0.07-0.47)	0.001

malnourished. Studies conducted elsewhere in India have also called for further research in evaluating the effect of nutrition in the progression of HIV.<sup>[22]</sup>

One of the main attributes to the social burden of HIV/AIDS is its stigma.<sup>[23]</sup> Patients try their best to conceal their infection status from their near and dear ones because of the fear of stigma. People fear that they might be ostracized from the society if their infection status is revealed. Measuring the contribution of stigma to the disease progression is a challenge. Patients hold the belief that they would face lesser stigma if their infection status is concealed.

Based on the prediction model that we have applied in this study, the interventions should be focused on three key areas in order to retard the progression of HIV infection. The first area should be the primary prevention of opportunistic infections. Oral candidiasis and fungal infections of nail can be considered as unfavorable outcomes for monitoring progression of disease. The occurrence of opportunistic infections can act both as a cause and an effect of progression of infection. The patients, their family members, and physicians should be

made aware of the influence of opportunistic infections in the progression of HIV. The second major area of focus is food and nutrition. The protein-rich food materials like legumes and eggs, green leafy vegetables, and lots of oral fluids were found to be protective. The patients should be made aware of the importance of diet from the outset itself. Third area is the social support system. Counseling by a professional is essential soon after the knowledge of their infection status. A multipronged approach is needed to fight social stigma. The patients should be equipped to cope up and fight against stigma and at the same time the authorities should focus on bringing about a change in the social outlook of the general public towards patients who are HIV positive.

## LIMITATIONS

One of the most serious limitations of this study is the inability to decide the temporal relationship between the study covariates and the study outcome. However, this has occurred partly because of the design of the study (a case control study in HIV/AIDS has got certain limitations because of the large window period and the delay in the identification of acute infection).<sup>[24]</sup> Also, a time delay would have happened between the actual time of progression to AIDS and its detection. The study has assumed that the cases and controls have a comparable time from the actual moment of infection to the moment of knowledge of their infection status.

## CONCLUSION

We examined the distal determinants of the progression including the psycho social factors, nutrition and stigma, which is studied less by the researchers. The importance of finding out these factors is that the civil society and administrators can take a lead role in the modification of these factors. The varied and enormous social dimensions of an HIV infection makes it the need of the hour.

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