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ASSESSMENT OF CHARACTERISTICS OF HIV CASES ASSOCIATED WITH PRESENTING WITH VERY POOR CLINICAL STAGE & CD4 COUNT

KEY WORDS: HIV, PLHIV, ART Centre, NACO, Multinomial logistic regression.

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ABSTRACT

Globally 34.0 million PLHIV, followed by an estimated burden of 2.4 million in India till 2011. It has been reported worldwide that HIV infected have tendency to delay in detection as well as in reporting that leads to increased risk of transmission and decreased survival. The present study was done to identify the characteristics associated with delayed presentation either at stage III or IV and further with CD4 count ≤ 350 cells /mm3.to ART centre.

Material& Method: - Out of all 4374 HIV positive confirmed aged ≥20 years cases identified during 2010 and 2011 and presented first at ART centre, SS Hospital, BHU, Varanasi within 180 days from the day of identification and further presenting with CD4 count investigation carried within 180 days, a total of 3419 cases reporting with CD4 count ≤ 350 cells /mm3 were considered in the present analysis to satisfy the objective. However, infections presented by the cases for the purpose of making comparisons all 4374 cases were taken with different categories of CD4 count. The characteristics of the cases considered were age, sex, weight, marital status, place of residence, mode of transmission, clinical stage, functional status and haemoglobin level at the time of first presentation.

Result :- Male and female ratio was 3:2; mostly (93.9%) below age 50 years. females were younger than males (37.8 ± 8.8 and 34.5 ± 7.9 years), female illiterate were 2.5 times more than male. Cases of stage I or II were 75.7%; statistically more males presented at stage III or IV than females.The CD4 count though carried with some delay after presentation, but of 50% in those carried within a week CD4 count was ≤100 cells/ mm3.The logistic regression analysis indicated that risk of presenting at stage III or IV is higher by about 3 times in males, 1.96 times higher in low weighing, 1.45 times higher in those with education at secondary level, but with reduced risk by half if transmission mode heterosexual. For Cases presenting at ART centre with CD4 count ≤ 350 cells /mm3 risk of late presenting was 3.41 times higher in males and 3.00 times higher in weighing ≤ 45 and 1.23 times higher in secondary level of education. Higher risk by 1.76 times was with either divorce or widow or separated compared to married; while lesser by half in unmarried.

Conclusion: - The primary responsibility of detection lies with the husband who is the driver of the disease, hence concentrated efforts at community awareness program should be made as the public health program that will be the key for early detection.

Introduction

Now a day's HIV infection has become worldwide a major concern of public health. The most affected is Sub-Saharan Africa (nearly 1 HIV infected in every 20 adults) followed by Caribbean and Eastern Europe and Central Asia (nearly 1 affected living adults); though both are observing continuous decline of new infections; sharpest of 42% in Caribbean and of 25% in sub-Saharan Africa from 2001 to 2011. While, several other countries e.g. Middle East and North Africa observing increase of more than 35% new infections [UNAIDS (2012)].

Excessive high mortality with poor survival is very common if antiretroviral therapy of HIV infected is not initiated timely [NACO 2009, Sabine Yerly et al (2000), Samet et al (2001), Zolopa et al (2009), Kumarasamy et al (2003)]. CD_4 count that is the basis of ART initiation drops very fast in absence of ART leading to many opportunistic diseases and death too [Lawn et al (2007)]. With low CD4 cell count the risk of Immune Reconstitution Inflammatory Syndrome (IRIS) is high and below 200/ml the risk of clinical symptoms and AIDS-defining illnesses increases substantially [Lawn et al (2007),Yeni et al(2002)].

Except female cases seeking antenatal care, majority of HIV infected present for identification only after appearance of the disease symptoms and further to ART centers for drug initiation. It is not necessary that the CD_4 cell count of the cases without symptoms is not low to its level of drug initiation. In the data it is observed that around 75% of the cases following WHO guide lines are in stage I & II, but were with CD4 count   350 cells /mm^3 at the time of presentation to ART centre.

Late HIV diagnosis and presentation to HIV care is very common throughout the globe, resulting significant HIV-related morbidity and mortality, even when ART is started promptly[Samet et al (2001),Battegay et al(2007),Girardi et al(2007),Gay et al (2006),Klein et al(2003),Gupta et al(2000),Chadborn et al(2005), Chadborn et al(2006), Nakashima et al (2003),Castilla et al(2002),Delpierre et al(2007),Dybul et al (2002),Girardi et al(2004), Hocking et al (2000),Manavi et al (2004),Sabin et al (2004),Wolbers et al (2008),Lawn et al (2007)] . Thus, early initiation of ART is of paramount and is of at most important to those knowing their sexual and use of Injectables behavior so as further progression can be delayed. Immune Reconstitution Inflammatory Syndrome (IRIS) that occurs at a higher frequency with low CD4 T cell counts can be prevented [Lawn et al (2007), Yeni et al (2002)].

India, because of its large population size though with low incidence carries the largest burden of HIV behind South Africa and Nigeria. Estimated 2.27 million people out of 1160 million populations were of age 15-49 years living with HIV during 2008, though declined compared to 2.31 million in 2007. Men are the single most powerful driving force due to their unprotected sex behavior with either paid sex/commercial workers or unprotected anal sex between men and IDU and these transmit HIV infection to more than 90% women.

The force to hide and to proceed late for identification and presentation to ART centre at least among men who know their behavior is social stigma. Eastern part of Uttar Pradesh with poor income and literacy is full of traditional values and social stigma; obviously presentation to ART centre will be much delayed. The

data of 2010-11 reveals that out of total 4374 presented cases 78.2% were with CD_4 count 350 cells /mm³ and among those with CD_4 count 350 cells /mm³ 36.9% were with CD_4 count 100 cells /mm³ i.e. overall 28.9%.

Presentation of cases with so less CD_4 count i.e. 100 cells /mm³ will have several opportunistic infections and even if ART is initiated to these, survival will be poor. The data reveals that the opportunistic infections among cases with CD_4 count 100 cells /mm³ was 1.36 times higher than those with CD_4 count > 100 cells /mm³ Thus, it is pertinent to analysis the variation of characteristics between those with CD_4 count 100 and 101 to 350 cells /mm³ and to identify the characteristics associated with reporting in adverse condition within the group need to be ART initiation.

Material & Method:
Out of all 4374 HIV positive confirmed aged 20 years cases identified during 2010 and 2011 and presented first at ART centre, SS Hospital, BHU, Varanasi within 180 days from the day of identification and further presenting with CD_4 count investigation carried within 180 days, a total of 3419 cases reporting with CD_4 count 350 cells /mm³ were considered in the present analysis to satisfy the objective. However, infections presented by the cases for the purpose of making comparisons all 4374 cases were taken with different categories of CD_4 count. The characteristics of the cases considered were age, sex, weight, marital status, place of residence, mode of transmission, clinical stage, functional status and haemoglobin level at the time of first presentation.

Statistical Analysis:
The data analysis was carried by SPSS Version 16.0. Initially overall as well as comparative frequencies by sex of the cases were analyzed. Further, statistical difference for various characteristics between the cases with CD_4 count 100 and 101 - 350 cells /mm³ was seen by simple bi-variate analysis. For some of the continuous variables, in addition to their categorical presentation mean and SD are also given. Finally, logistic regression analysis was carried to identify the real associated characteristics along with their strength of association to present at ART centre very late i.e. in a very adverse condition. A p-value < 0.05 was considered as statistically significant.

4.2. B.4: Observations and results
Overall HIV cases suffering from any of the opportunistic infections at first presentation to ART centre was highest (17.1%) in those with CD_4 count ≤100 cells /mm³ followed by 12.7% in those with CD_4 count 101-350 cells /mm³; while in very less cases (≤ 1.5%) with CD_4 count 350 – 500 and >500 cells /mm³ respectively. Overall major infection at presentation was tuberculosis (7.0%) and was almost double in cases with CD_4 count ≤100 than 101-350 cells /mm³. Skin infection was also in 2.5% and 1.9% in HIV cases presenting with CD_4 count ≤100 and 101-350 cells /mm³ respectively. Among the cases presented with CD_4 count ≤100 and 101-350 cells /mm³ 26.8% and 19.8% developed tuberculosis during the period of follow up observation compared to only 4.8% and 2.9% with CD_4 count 350 – 500 and >500 cells /mm³ respectively.

As evidenced in Table-2, in 3419 cases with CD_4 count 350 cells/ mm³, the ratio of male and female HIV cases was approximately 1.8:1. Overall average age of cases is 37.2 years with SD = 8.6 years; female cases are relatively younger (35.3±8.0) than male cases (38.2 ± 8.7). Mostly (93.6%) cases are of the most productive age group i.e. below the age of 50 years and about half (52.2%) were much young i.e. below the age of 35 years. Female presenting cases below the age of 35 years were significantly much higher (62.3%) than male cases (46.5%); while between the age 35-50 years male cases were significantly much higher (45.7%) than female cases (33.3%). Overall, nearly one third (35.5%), 25.4% and 33.8% cases were illiterate, primary and secondary level education; only few (5.3%) were of college level education. Illiterate females were about 2.5 times higher than illiterate males; while secondary level males were 2.5 times higher

than secondary level females. Among male cases, 84.2% were married; while among female cases married were much less (58.1%). Though, unmarried cases were very less (5.0%), but compared to female cases male cases were 3 times higher than females. Much of the cases (about 20%) were either divorced or separated or widowed and these were female cases in majority (about 40%) compared to only 9.2% male cases. Overall 53.8% and 33.5% cases presenting were from within 100 km and 100-200 km respectively; only nearly 10% cases were of Varanasi. The male female presentation was almost similar irrespective of place of residence, though within 100 km of distance statistically more females than males were presenting, but the difference was of only 4.5%. Overall, nearly half and half of the cases were with weight 45 kg and > 45 kg, but female cases with weight 45 kg were higher by more than 1.7 times than male cases. Overall, mode of transmission of three fourth cases (77.0%) was heterosexual and significantly much higher (86.2%) in females than males (71.8%). While Injectables was significantly higher in males than females, but these were very few (over all 5.4%). The mode of transmission was not elicited by 17.6% of the cases and was almost 2.25 times higher in males than females. Overall clinically more than three fifth (63.8%) cases presented at stage I; very few 7.5% of stage II and more than a quarter (28.7%) at stage III or IV. Significantly much more (74.8%) female cases compared to 57.7% male cases were of stage I and much more (34.4%) male cases compared to 18.3% female cases were in stage III or IV. Overall nearly ninety percent (89.5%) cases presenting were working, only 10.5% cases either ambulatory or bed ridden. Ambulatory or bed ridden male cases were twice (13.0%) of the female cases (6.0%). Overall 36.9% cases presented in a very adverse condition i.e. CD_4 count 100 cells/mm³; while rest between 101-350 cells/mm³. The presentation of cases with CD_4 count 100 cells/mm³ was significantly much higher **(**42.6%) in males than females (26.7%). Cases for their hemoglobin level below 9 gm/dl are only 9.7% and almost similar for both male and female cases; while female cases were higher by 8.0% compared to 36.5% male cases for the hemoglobin level between 9.0-11.0 gm/dl and visa vise male cases were higher by 8.9% compared to 45.2% female cases for their hemoglobin level ≥ 11 gm/dl.

The HIV cases with CD_4 count ≤ 100 cells/ mm³ are likely to suffer more with IRIS and has poor survival even put on ART. Hence, within the ART cases, those presenting with CD_4 ≤ 100 cells/ mm³ for the first time treated as very late presenter and between 101-350 cells/ mm³ as late presenter for ART initiation. The variation of characteristics of very late presenter for drug initiation was seen and is presented in Table-3.

The proportions of very late male presenting ART cases i.e. with ≤ 100 cells/ mm³ CD_4 count in different age groups, were statistically same around two fifth in each age group (2 = 4.12, df = 2, p = 0.127); while among females such cases were increasing from 24.4% in the age group 35 years to 29.6% in the age group 36-50 years and further to 37.0% in the age group >50 years (2 = 6.63, df = 2, p= 0.036). Male late ART presenters were significantly higher by about 15% than female cases in the age groups ≤ 35 years and 36-50 years respectively (p <0.0001); while almost same in both the sexes for the age group >50 years. The male cases with CD_4 count ≤ 100 cells/ mm³ were about half (53.0%) for their weight ≤45 kg at presentation; while significantly much less (34.5%) for their weight >45 kg (2 = 75.44, df = 1, p <0.0001). Similarly, significantly more female cases with CD_4 count ≤ 100 cells/ mm³ were presenting with lesser weight i.e. ≤45 kg i.e. 30.7% compared to 15.8% with weight > 45 kg (2 = 27.31, df = 1, p <0.0001). It is also evident that significantly more male cases presented very late i.e. with CD_4 count ≤100 cells/ mm³ irrespective of their weight (p < 0.0001).

Presentation of cases with CD_4 count ≤ 100 cells/ mm³ was highest (46.0%) among ART cases of secondary level education and lowest (38.3%) among primary level (38.7%). Education of male cases showed association with very late presentation i.e. CD_4 count ≤ 100 cells/ mm³. While presentation of female cases with CD_4

count $\leq$ 100 cells/ mm^3 was statistically similar irrespective of their level of education. Presentation of cases with CD$_4$ count 100 cells/ mm^3 was significantly higher among male cases than female cases in the entire educational category except in those with college level education (p < 0.0001). Presentation of male cases among ART cases very late i.e. with CD$_4$ count 100 cells/ mm^3 was not associated with their marital status and was almost 42% respective marital status category (2 = 0.12, df = 2, p =0.933); the same was also true in female cases, but unmarried's were much low (7.4%) in CD$_4$ count category 100 cells/ mm^3 compared to 27% each of other categories of marital status (2 = 5.45, df = 2, p =0.066). Though, very late presenter among females were significantly lesser than male cases (p < 0.0001), male cases were about 6 times higher among unmarried. No statistical association of cases presenting very late i.e. CD$_4$ count 100 cells/ mm^3 was seen with their place of residence in both the sexes (for male cases 2 = 3.50, df = 3, p =0.320 and for female cases 2 = 1.49, df = 3, p =0.685). But male cases presenting with CD$_4$ count 100 cells/ mm^3 were significantly higher by about 1.5 times in all the categories of their place of residence except those of >200 km from Varanasi. In both the sexes, very late presentation of cases was found associated with their mode of transmission (p < 0.0001 for male cases and < 0.007 for female cases). Among both the sexes' very late presenters were those who did not elicit mode of transmission; highest 53.4% in males and 38.7% in females. Very late presenters among those with mode of transmission unsafe Injection is slightly higher among males than females; while these were about 1.5 times higher in males if mode of transmission was heterosexual or unknown (p < 0.05). ART cases presenting very late i.e. CD$_4$ count 100 cells/ mm^3 were increasing significantly in both the sexes as one move from lower stage to higher stage; lowest 34.8% at stage I and highest 55.6% at stage III/IV among males and lowest (19.3%) and highest (50.9%) among females. Very late presentation of male cases with CD$_4$ counts 100 cells/ mm^3 at stage I is statistically more than 1.5 times higher than female cases (p < 0.0001); while almost similar at stage II and slightly higher in stage III/IV. Cases presenting very late i.e. with CD$_4$ count 100 showed significant association with their functional status in both the sexes (p < 0.0001). Presentation of male cases with CD$_4$ count 100 cells/ mm^3 was more than 1.5 times higher if the case was ambulatory or bedridden than those of working; while female cases presentation with CD$_4$ count 100 cells/ mm^3 was more than 2.5 times higher if the case was ambulatory or bedridden than those of working. Male and female cases with CD$_4$ count 100 cells/ mm^3 presenting in ambulatory or bedridden condition were statistically same and were more than 60% while these were significantly 1.5 times higher in male working cases than female working cases (p < 0.0001). Level of hemoglobin did show statistical association with very late presenters, cases in both the sexes presenting with CD$_4$ count 100 cells/ mm^3 was significantly decreasing as hemoglobin level was increasing (P<0.0001). Compared to female cases, male cases presenting very late were statistically more than 1.5 times higher in each category of (p < 0.0001).

The results indicated in bivariate analysis, either showing association or not, may not be always true due to presence of confounding effect; hence logistic regression analysis was carried by taking all the characteristics of the ART cases. From among the considered characteristics e.g. sex, age, educational level, place of residence, weight, marital status, mode of transmission, clinical staging and haemoglobin level of the cases; only sex, educational level, weight, place of residence, mode of transmission, clinical staging and hemoglobin level emerged as the significantly associated characteristics to presenting very late to ART centre. Among the ART cases very late presentation was 2.03 times (CI: 1.68 – 2.46) higher in male cases than female cases. Very late presentation was similar among college level, primary level compared with illiterates; while in cases very late presentation was 1.25 times (CI: 1.03 - 1.52) higher in cases having secondary level education. The cases of HIV who are very late presenter when compared for their place of residence in reference to cases of Varanasi, those presenting very late from distance within 100km

and 100 km – 200 km were almost similar; while those presenting from beyond 200 km, risk of very late presentation was 1.66 times (CI: 1.05 – 2.63). The risk of very late presentation was twice (CI: 1.70 - 2.34) times higher among ART cases whose weight at the time of presentation was 45 kg than those with weight > 45 kg. Mode of transmission was strongly associated with very late presentation of the cases. Compared to cases who did not or could not elicit their mode of transmission, the risk of very late presentation was lesser by one third (OR: 0.69; CI: 0.57 - 0.84) in those whose mode of transmission was heterosexual and by half (OR: 0.48; CI: 0.33 - 0.70) in those of Injectables. The risk of very late presentation was 2.35 (CI: 1.99 – 2.77) and 1.89 (CI: 1.44 - 2.48) times higher in cases who were presenting in stage III/IV and stage II respectively, compared to those presenting in stage I. Hemoglobin level also showed strong association with very late presentation. The risk of very late presentation was 1.90 (CI: 1.47 – 2.47) and 1.26 (CI: 1.07 - 1.48) times higher in cases whose hemoglobin level was below 9 mg/dl and between 9-11 mg/dl respectively.

Discussion
Late presentation is universal and cases presenting at very low CD$_4$ counts is alarmingly high in both developing and developed nations [Girard et al (2004), Tuboi et al (2007),Chadborn et al (2006)]. Earlier presentation of HIV infected reflects their self-perceived risk or universal screening [Wortley et al (1995)]. Immune Reconstitution Inflammatory Syndrome (IRIS) occurrence is at a higher frequency in cases with low CD4 T cell count and IRD was found strongly associated with early ART initiation and low CD4 cell count [Casseb et al (2003)]. Hence for IRIS prevention early detection and early ART initiation is the prerequisite [Lawn et al (2007),Yeni et al(2002),Casseb et al (2003)]. Other advantages of early ART initiation are to reducing the risk of transmission and increasing the survival of the infected, but one should present well in time before reaches very less CD$_4$ count.

Males are the main drivers of HIV infection and always hiding their behavior and disease due to social stigma and are presenting very late. Females, getting infection from their husband/sex partner and unless attended for ANC, also present late as being unaware of the status of partner and present only when the infection manifested to disease condition. The Eastern part of Uttar Pradesh is with low literacy, full of social taboos and stigma and since the mode of transmission is mostly heterosexual as also indicated by data; most of the males infected for HIV infection in their adverse condition because hiding the disease; true also for females except few identified during the course of antenatal care. The data reveals that 78.17% cases are presenting to ART centre when really need ART initiation i.e. CD$_4$ count 350 cells/ mm^3 or below and out of these 36.94% are presented with CD$_4$ count 100 cells/ mm^3 or below. The analysis was carried to assess the variation of various presenting infections with varying CD$_4$ count and to examine the variation of different characteristics between male and female HIV cases presenting first time to ART centre at the stage when ART need to be initiated. Further, the associations of the characteristics of the cases for both the sexes was assessed and differentials between the sex for each of the characteristics of the cases presenting with very late i.e. with CD$_4$ count 100 cells/ mm^3 was seen. Finally, logistic regression analysis was carried to identify the characteristics associated with presentation of cases with CD$_4$ count 100 cells/ mm^3 i.e. presenting very late among those who had reached the stage of ART initiation. The cases taken are those registered during the year 2010-11 at the ART Centre of tertiary care SS Hospital, IMS, BHU.

The opportunistic infections in cases with CD$_4$ count 100 cells /mm^3 was among 17.1% followed by 12.7% among those with CD$_4$ count 101-350 cells /mm^3 and very few (nearly 1.5%) with CD$_4$ count 350 – 500 and >500 cells /mm^3. Major infection at presentation was tuberculosis (7.0%) and mostly among those with CD$_4$ counts 100 and 101-350 cells /mm^3. Tuberculosis at presentation was almost double in those with CD$_4$ count 100 cells /mm^3 compared to cases with CD$_4$ count 101-350 cells /mm^3;

suggesting many of the infections can be prevented if HIV cases can report timely to health care. Among the cases presenting with CD_4 count 100 and 101-350 cells /mm^3 26.8% and 19.8% developed tuberculosis during the period of observation compared to only 4.8% and 2.9% in those with CD_4 count 350 – 500 and >500 cells /mm^3 respectively. The observations indicate that early presentation of cases requiring ART will definitely avoid many infections and development of tuberculosis along with IRIS. Study of south India reported pulmonary tuberculosis (49%), much higher than present study, pneumocystis carinii pneumonia (6%), cryptococcal meningitis (5%), and central nervous system toxoplasmosis (3%) being the most common acquired immune deficiency syndrome. The study also reported 19 times (CI: 5.56-64.77) higher mortality in cases with a CD4 lymphocyte count <200 cells/microL than those with CD4 cell count of >350 cells/microL. Patients who had 1 opportunistic infection were 2.6 times more likely to die than those who did not have an opportunistic infection; It was further observed that patients with low CD_4 lymphocyte counts improved the odds of survival (OR = 5.37; CI: 1.82-15.83) when were put on Antiretroviral therapy [56]. Nearly one third cases presenting with very less CD_4 count are definitely to suffer with poor survival.

Among the 3419 cases presenting first time at ART stage, the ratio of male and female cases was approximately 1.8:1; female cases were relatively younger by almost 3 years than male cases (average age of females: 35.3 8.0 years and of males: 38.2 ± 8.7 years). Mostly (93.6%) cases were of the most productive age group i.e. below the age of 50 years and about half (52.2%) were much young i.e. below the age of 35 years. Female presenting cases below the age of 35 years were significantly much higher (62.3%) than male cases (46.5%); while between the age 35-50 years male cases were significantly much higher (45.7%) than female cases (33.3%). Irrespective of sex the families of the cases of productive age group naturally have to face severe mental stress and financial loss. Nearly one third (35.5%) cases were illiterate while quarter of the cases (25.4%) had primary level schooling; only few (5.3%) were with college level education. Illiterate females were much higher (about 2.5 times) than males; while in secondary level education males were 2.5 times higher than females. Most affected are lower levels of education that is in accordance to educational status of rural part. More than 80% (84.2%) males presenting were married; while against males 58.3% female cases were married. Unmarried cases were though only 5.0%, but unmarried male cases were 3 times higher than female cases. As high as, about 4 times female cases (39.7%) were either divorced or separated or widowed than male cases. The gap observed between male and female cases for marital status may be female cases might have lost their husband due to death from HIV. Mostly (87.3%) cases were within 100 km or 100-200 km from Varanasi, only about 10% cases were of Varanasi; presentation of cases in both the sexes was similar irrespective of their place of residence.

Nearly half and half cases were with weight 45 kg and > 45 kg; but female cases presenting with weight 45 kg were higher by more than 1.7 times than male cases. Of about three fourth (77.0%) cases, transmission mode was heterosexual and significantly higher (86.2%) in females than males (71.8%). Injectables as the mode of transmission though only in 5.4% cases, but significantly higher in males than female cases. Cases not elicited the mode of transmission irrespective of any reason either unaware or hiding due to social stigma was in 17.6% and almost 2.25 times higher in male than female cases. Since the transmission in rural set up among females is manly from husband's who acquire infection through their illegitimate relations especially from high risk group, hence instead to disclose the mode of transmission usually state unknown cause. Overall 63.8% cases presented at clinical stage I; few 7.5% at stage II and more than a quarter (28.7%) at stage III/IV; presentation at stage I was higher of female cases (74.8%) than male cases (57.7%). While, presentation at latter stages i.e. III/IV was higher of male cases (34.4%) than female cases (18.3%). In fact a significant proportion of females are identified much earlier during their ANC

hence more presentation of female cases at stage I and lesser at latter stages. Among ART presenting cases, overall only 10.5% cases were either ambulatory or bed ridden; but male cases were more than twice compared to 6.0% female cases; it is only in fact due to hiding tendency of the disease. More than one third cases at presentation were with CD4 count 100 cells/mm^3 and such cases were more than 1.5 times higher in males compared to 26.7% female case. It is clearly reflecting males will have poor survival and widowhood is likely to increase that will fall the whole family to a great agony. ART cases for their hemoglobin level below 9 gm/dl are only 9.7% and almost similar in both sexes; while female cases were higher by 8.0% compared to 36.5% male cases for their hemoglobin level between 9.0-11.0 gm/dl and visa vise male cases were higher by 9.1% compared to 45.2% female cases for their hemoglobin level 11 gm/dl. The variation of characteristics of ART cases in relation to CD_4 count by categorizing them into two groups; one with CD_4 100 cells/ mm^3 so called very late presenter and between 101-350 cells/ mm^3 called late presenter indicated that the proportions of male cases presenting very late i.e. 100 cells/ mm^3 are statistically same around 40% in each age group (2 = 4.12, df = 2, p = 0.127); while among females such cases are increasing from 24.4% in the age group 35 years to 29.6% in the age group 36-50 years and further to 37.0% in the age group >50 years (2 = 6.63, df = 2, p= 0.036). Since, females are also identified during ANC services and higher aged females are less likely to be pregnant and availing ANC services. Very late male presenters are significantly higher by about 15% than female cases in the age groups 35 years and 36-50 years respectively (p <0.0001); while almost same in both the sexes for the age group >50 years. As stated above it is due to the fact that younger age group female are likely to bear children and are identified during the course of ANC; as age of female increases child bearing likelihood reduces and therefore at higher age male female cases presenting with CD_4 100 cells/ mm^3 are almost same.

The male cases with CD_4 count 100 cells/ mm^3 were about half (53.0%) for their weight 45 kg at presentation; while in those with weight >45 kg cases with CD_4 count 100 cells/ mm^3 are significantly much less (34.5%) (2 = 75.44, df = 1, p <0.0001). Similarly, significantly more female cases (30.7%) with CD_4 count 100 cells/ mm^3 are presenting with lesser weight i.e. 45 kg compared to 15.8% with weight > 45 kg (2 = 27.31, df = 1, p <0.0001). The findings are indicating that lower is the CD_4 count higher is the likelihood of loss of weight. It is also evident that significantly more male cases than female cases are presenting very late irrespective of their weight (p < 0.0001). Presentation of cases with 100 cells/ mm^3 CD_4 count is highest (46.0%) among ART cases of secondary level education and lowest (38.7%) among primary level; education of male cases did show association with late presentation i.e. below CD_4 count 100 cells/ mm^3. Very late presentation among female cases was statistically similar irrespective of level of their education (2 = 0.70, df = 3, p =0.872). Presentation of cases with CD_4 count 100 cells/ mm^3 is significantly higher among male cases than female cases in the entire educational category; indicating males are hiding the disease and presenting only after the disease condition is poorer. Very late presentation of males among ART cases is not associated with their marital status and is almost in 42% cases (2 = 0.12, df = 2, p =0.933); true of female cases, though among unmarried females very late presentation was only by 7.4% compared to more than 25% among married and divorced/separated/widowed (2 = 5.45, df = 2, p =0.066). Very late presenter among female ART cases are significantly lesser than male cases (p < 0.0001) in each category of marital status; compared to female cases very late male presenters were about 6 times and more than 1.5 times higher in unmarried and divorced/separated/widowed male cases; this may be perhaps due to confounding effect.

In both the sexes very late presenters were not associated with their place of residence (2 = 3.50, df = 3, p = 0.320 for males and 2 = 1.49, df = 3, p = 0.685 for females); however, late presenters were much higher in both the sexes if belonging to the farther places. Very less female presenters were significantly lesser than

male presenters for each defined category of place of residence. Mode of transmission did show highly significant association in both the sexes (2 = 33.11, df = 2, p <0.0001 for males and 2 = 9.89, df = 2, p = 0.007 for females); very late male presenters were lowest 31.9% among unsafe Injectables users that increased to 40.2% in heterosexuals and further to 52.1% who stated unknown mode of transmission. While very late presenters among females were almost same of whom mode of transmission was Injectables and heterosexual but significantly higher (38.7%) who stated unknown mode of transmission. Higher proportion of cases eliciting unknown causes was definitely hiding the disease and still due to social values are not disclosing. Compared to very late female presenters, male presenters were significantly higher by 15% eliciting mode of transmission heterosexual and not known; while almost same among Injectable users. ART cases presenting very late i.e. CD_4 count $\leq$ 100 cells/ mm^3 were increasing significantly in both the sexes with the increase of disease stage (2 = 83.97, df = 2, p <0.0001 for males and 2 = 103.90, df = 2, p < 0.0001 for females). At stage II and stage III/IV, both male and female very late presenters were almost same (nearly 40% at stage II and nearly 50% at stage III/IV), but at stage I very late male presenters were 1.7 times higher than females. Obviously cases presenting with CD_4 count $\leq$ 100 cells/ mm^3 will show significant association with their functional status in both the sexes (p < 0.0001). Presentation of very late in both male and female cases was almost same and more than 60% when presenting in ambulatory or bedridden condition; but among cases in working conditions, significantly 1.5 times more males than females cases were very late presenter (p < 0.0001). Level of hemoglobin did show statistical association with very late presenting cases in both the sexes; as hemoglobin level was increasing very late presenters were decreasing (p < 0.0001); indicating at lower CD_4 count hemoglobin level also goes down.

The results indicated in bivariate analysis, either showing association or not, may not be always true due to presence of confounding effect; hence logistic regression analysis was carried by taking all the characteristics of the ART cases. From among the considered characteristics e.g. sex, age, educational level, place of residence, weight, marital status, mode of transmission, clinical staging and haemoglobin level of the cases; sex, education level, place of residence, weight, mode of transmission, clinical staging and hemoglobin level emerged as the significantly associated characteristics to presenting very late to ART centre. Age has not emerged as the contributor to late presentation, though one study had shown that higher aged are the late presenter [kumarasamy et al (2003)].

Among the ART cases very late presentation was 2.03 times (CI: 1.68 – 2.46) higher in male cases than female cases, indicating that men due to social stigma are hiding the disease and report only when the disease is manifested in severe form. On the contrary, women are in majority identified early during their anti-natal checkup, so by the time their CD_4 count has not come down are reporting. It has been observed that people with AIDS at entry were 5 times more likely to die during this period compared to patients who were asymptomatic at entry (*p* = 0.006) and women had shown better outcomes than men, reflecting differences in $CD4^+$ T-cell counts at study entry[HIV-CAUSAL collaboration et al (2010)]. Very late presentation was similar among college level and primary level compared with illiterates; while in cases very late presentation was 1.25 times (CI: 1.03 - 1.52) higher in cases having secondary level education. There is no basic difference between illiterates and primary level of education and inspite of prevailing social stigma are reporting early. Further since college level cases are more aware of severity of the disease, get identified and report in early condition of the disease. But, the cases that are secondary level education; mostly are migrants and inspite of knowing their sexual behavior due to social stigma go for late HIV testing and reporting very late when the disease condition is beyond control. Very late presentation of cases of HIV who are in the stage of initiation of ART when compared for their place of residence in reference to cases of Varanasi, those presenting very late from distance within 100 km and 100 km – 200 km were

almost similar; while those presenting from beyond 200 km risk of very late presentation was 1.66 times (CI: 1.05 – 2.63). Certainly, the distance from the health care delivery system is affecting to report very late, suggestive of such services be access to nearby. But another considerable aspect is of much importance that since social stigma is associated with this disease, people may not be turning to avail the services nearby their place of residence. The risk of very late first presentation was seen 2.00 (CI: 1.70 - 2.34) times higher among ART cases whose weight at the time of presentation was   45 kg than those with weight > 45 kg. Obviously, if the CD_4 count is very less, cases may suffer with many opportunistic infections and loss of appetite will loosen their weight. Mode of transmission was strongly associated with very late presentation of the cases. Compared to cases that did not or could not elicit their mode of transmission, the risk of very late presentation was lesser by one third (OR: 0.69; CI: 0.57 - 0.84) in those whose mode of transmission was heterosexual and by half (OR: 0.48; CI: 0.33 - 0.70) in those using unsafe Injectables. The obvious reason is that the cases whose mode of transmission was either heterosexual or use of Injectables knew their risk behavior and due to perception of consequences reporting in better condition i.e. before reaching the worst level of their CD_4 count; while those stating unknown cause majority may be the hider of their behavior. The risk of first presentation was 2.35 (CI: 1.99 – 2.77) and 1.89 (CI: 1.44- 2.48) times higher in cases who were presenting in stage III/IV and stage II respectively, compared to those presenting in stage I. The result indicates that CD_4 count of cases is more likely to be below 100 cells /mm^3 and are at higher risk of IRIS are in need of anti-retroviral therapy and require cART initiation. Significantly more cases are anemic while reporting with CD_4 count $\leq$100 cells /mm^3(OR = 1.90, CI: 1.47 – 2.47 and OR = 1.26, CI: 1.07 – 1.48 among cases with hemoglobin level < 9 mg/dl and between 9-11 mg/dl). It has been empirically shown that cART had halved the average mortality rate in HIV-infected individuals and mortality reduction was greater in those with worse prognosis at the start of follow-up [Kumarasamy et al (2003)]. As demonstrated that mortality was 19 times (CI: 5.56-64.77) higher in cases with a CD_4 lymphocyte count <200 cells/microL than those with CD4 cell count of >350 cells/microL; patients who had 1 opportunistic infection were 2.6 times more likely to die (CI: 0.95-7.09) than those who did not have an opportunistic infection and patients with low CD_4 lymphocyte counts improved the odds of survival by 5.37 times (OR = 5.37; CI: 1.82-15.83) when were put on Antiretroviral therapy [56], the cases with very low CD_4 count are likely to suffer with many opportunistic infections and survival will be poor if ART initiation is delayed. Such type of message in media may aware the people who are at risk behavior of HIV.

Conclusion:
The risk of several infections including tuberculosis at presentation and after presentation in due course of time is much higher with late presenter i.e. CD_4 count $\leq$ 100 cells /mm^3 and these are mostly males, of distant places, of lower weight and clinically of higher stages; such cases are likely to face poor survival. Community needs change of behavior, if not, protective sex be adopted and in case any suspicion of acquiring HIV infection immediate testing be done before reach IRIS condition for better survival and for that only awareness can make the dent in overcoming such situation.

Table-4.2.B.1: Opportunistic infections at presentation with varied levels of CD_4counts

Opportunistic Infections	Cd4 Count (cells /mm^3)				Total (N=4374)
	<100 (N=1263)	101-350 (N=2156)	350-500 (N=478)	>500 (N=477)	
Any infection Present at presentation	17.1	12.7	1.3	1.5	11.5
TB	12.0	6.7	0.8	1.0	7.0
Skin Infection	2.5	1.9	0.2	0.0	1.7
Genital	0.4	0.6	0.2	0.0	0.4
Diarrhea	1.3	1.3	0.2	0.0	1.1
Others*	2.1	3.0	.0	0.4	2.1

Developed TB after presentation	26.8	19.8	4.8	2.9	18.3

* URTI, LTRI, cold cough, fever, vomiting, typhoid, viral, weight loss, weakness

Table-4.2.B.2: Background characteristics of cases with CD4 count less than 350 cells /mm3 at presentation to ART Centre

Characteristics	Male (2198)	Female (1221)	Total (3419)	p-value
Age (yrs)				
= 35	46.5	62.3	52.2	<0.0001
36-50	45.7	33.3	41.3	<0.0001
> 50	7.8	4.4	6.4	<0.0001
Mean ± SD (Inter Quartile Range)	38.2±8.7 (32-45)	35.3±8.0 (30-40)	37.2 ± 8.6 (30 – 42)	<0.001
Educational status				
Illiterate	22.3	59.4	35.5	<0.0001
Primary School	28.3	20.2	25.4	<0.0001
Secondary School	43.1	17.0	33.8	<0.0001
College & above	6.3	3.4	5.3	<0.0001
Marital status				
Married	84.2	58.1	74.9	<0.0001
Unmarried	6.6	2.2	5.0	<0.0001
Divorced/ Widowed/Separated	9.2	39.7	20.1	<0.0001
Place of Residence (km)				
Varanasi	9.4	8.8	9.2	0.279
Within 100 km from Varanasi	52.2	56.7	53.8	0.006
Between 100 - 200 km from Varanasi	34.6	31.9	33.5	0.054
>200 km from Varanasi	3.8	2.8	3.5	0.054
Weight (kg)				
= 45	43.8	73.1	54.2	<0.0001
>45	56.2	26.9	45.8	<0.0001
Mean ± SD (Inter Quartile Range)	47.6±8.7 (41-53)	40.1±7.5 (35-45)	44.9 ± 9.1 (39 - 50)	<0.0001
Mode of transmission				
Heterosexual	71.8	86.2	77.0	<0.0001
Unsafe Injection	6.1	4.0	5.4	0.003
Unknown	22.1	9.8	17.6	<0.0001
WHO clinical staging				
Stage-I	57.7	74.8	63.8	<0.0001
Stage-II	7.9	6.9	7.5	0.140
Stage- III/IV	34.4	18.3	28.7	<0.0001
Functional status				
Working	87.0	94.0	89.5	<0.0001
Ambulatory/ Bed ridden	13.0	6.0	10.5	<0.0001
CD4 count (cells/mm³)				
=100	42.6	26.7	36.9	<0.0001
101-350	57.4	73.3	63.1	<0.0001
Mean ± SD (Inter Quartile Range)	134.7 ± 89.4 (59-200)	176.8 ± 97.1 (93-252)	149.7 ± 94.4 (67– 223)	<0.0001
Hemoglobin (gm/dl)				
< 9	9.4	10.3	9.7	0.200
9-11	36.5	44.5	39.4	<0.0001
= 11	54.1	45.2	50.9	<0.0001
Mean ± SD (Inter Quartile Range)	11.0±1.7 (10.1-12.0)	10.7±1.6 (10.0-11.7)	10.9± 1.7 (10.0 – 11.9)	<0.0001

Table-4.2.B.3: Variation of characteristics of male and female cases presenting very late (CD4 count   100 cells/mm3) at presentation to ART centre

Characteristics	Male Cases		Female Cases		
	Number (n=2198)	CD4 count =100	Number (n=1221)	CD4 count =100	Z and P values
Age (yrs)					
= 35	1023	41.6	761	24.4	<0.0001
36-50	1005	44.6	406	29.6	<0.0001
> 50	170	37.1	54	37.0	>0.476
χ2, df, p value	4.12,2,0.127		sss6.63,2,0.036		
Weight (Kg)					
>45	1236	34.5	329	15.8	<0.0001
=45	962	53.0	892	30.7	<0.0001
χ2, df, p value	75.44,1,<0.0001		27.31,1,<0.0001		

Educational status					
Illiterate	490	41.6	725	26.1	<0.0001
Primary school	622	38.7	247	27.9	<0.0001
Secondary school	948	46.0	207	28.0	<0.0001
College	138	40.6	42	23.8	<0.0001
χ^2, df, p value	8.65,3,0.034		0.70,3,0.872		
Marital status					
Married	1851	42.5	710	27.6	<0.0001
Unmarried	144	43.8	27	7.4	<0.0001
Divorced /Separated/ Widowed	203	43.3	484	26.4	<0.0001
χ^2, df, p value	0.12,2,0.933		5.45,2,0.066		
Place of Residence					
Varanasi	207	41.5	107	28.0	<0.0001
Within 100 km from Varanasi	1147	42.5	692	26.2	<0.0001
Within 200 km from Varanasi	760	42.0	388	26.5	<0.0001
>200 km from Varanasi	84	52.4	34	35.3	<0.0001
χ^2, df, p value	3.50,3,0.320		1.49,3,0.685		
Mode of Transmission					
Heterosexual	1578	40.2	1053	25.3	<0.0001
Unsafe Injection	135	31.9	49	28.6	< 0.05
Unknown	485	53.4	119	38.7	<0.0001
χ^2, df, p value	33.11,2,<0.0001		9.89,2,0.007		
Clinical staging					
I	1269	34.8	913	19.3	<0.0001
II	173	43.9	84	42.9	>0.25
III/IV	756	55.6	224	50.9	< 0.01
χ^2, df, p value	83.97,2,<0.0001		103.90,2,<0.0001		
Functional Status					
Working	1912	39.7	1148	24.3	<0.0001
Ambulatory/Bedridden	286	62.2	73	64.4	0.22, > 0.05
χ^2, df, p value	51.69,1<0.0001		56.33,1<0.0001		
Hb (mg/dl)					
<9	206	63.1	126	43.7	2.81, <0.0001
9-11	803	46.9	543	26.0	6.21, <0.0001
>11	1189	36.2	552	23.6	5.80, <0.0001
χ^2, df, p value	61.76,2, <0.0001		21.45,2, <0.0001		

Table-4.2.B.4: Risk factors involved for very late presentation (CD4 Count < 100 cells /mm³) in reference to CD4 count > 100 cells /mm³

Characteristics	β	Wald statistic	p-value	Adjusted odds ratio	95% confidence interval
Sex					
Male Female	0.71	22.48	<0.0001	2.03	1.68 – 2.46
Age					
=35	0.05	0.10	0.757	1.05	0.77 - 1.43
35-50	0.22	1.97	0.160	1.25	0.92 - 1.71
>50	-	-	-	-	-
Education					
College & above	0.03	0.03	0.860	1.03	0.72 - 1.48
Secondary school	0.22	5.24	0.022	1.25	1.03 - 1.52
Primary School	-0.07	0.40	0.528	0.94	0.77 - 1.15
Illiterate	Ref.	-	-	-	-
Place of Residence					
>200 km	0.51	4.68	0.030	1.66	1.05 – 2.63
100 km to 200 km	0.04	0.07	0.795	1.04	0.80 – 1.37
Within 100 km Of Varanasi	0.06 Ref.	0.20	0.651	1.06	0.82 – 1.39
Weight (kg)					
=45	0.69	71.56	<0.0001	2.00	1.70 - 2.34
>45	Ref.	-	-	-	-

Marital Status					
Divorce/widow/separated	-0.07	0.43	0.511	0.93	0.76 - 1.15
Unmarried	-0.07	0.14	0.711	0.94	0.67 - 1.32
Married	Ref.	-	-	-	-
Mode of Transmission					
Heterosexual	-0.37	16.48	<0.0001	0.69	0.57 - 0.84
Injectables	-0.73	14.64	<0.0001	0.48	0.33 - 0.70
Not Stated	Ref.	-	-	-	-
Clinical staging					
III/IV	0.85	100.91	<0.0001	2.35	1.99 – 2.77
II	0.64	20.59	<0.0001	1.89	1.44 - 2.48
I	Ref.	-	-	-	-
Hb (mg/dl)					
<9	0.64	56.62	<0.0001	1.90	1.47 – 2.47
9-11	0.23	8.08	0.004	1.26	1.07 – 1.48
>11	Ref.				