

CD4+ Cell Count in the HIV/AIDS-infected People with Pulmonary Complications

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Abstract: ***Introduction:** Pulmonary complications are very common during the course of Acquired Immunodeficiency Syndrome (AIDS). **Aim of the study:** The main study goal is to assess the patterns of respiratory complications in the HIV/AIDS patients. **Materials and methods:** In the study are enrolled 77(83.1%male HIV/AIDS)patients with pulmonary complications,with the mean age of the subjects was 46.4±10.2, and known as HIV seropositive patients from 5.1 ±2.4. years .Data are elaborated by SPSS17. **Results:** By occupational,29(37.7%) were unemployed,22(28.6%), employed,5 (6.5%), farmeres,7(9.1%) office-bearers,14(18.2%). the others,regard to the count of CD4 cellules, 6(7.8%) from 300-399 cel/ml,15(19.5%) with 200-300 cel/ml,28 (36.4%) patients from 100-199 cel/ml, and 28(36.4%) <100cel/ml. In all of the patients(77) with HIV/AIDS are found 84 pulmonary manifestations, respectively bacterial pneumonia(first episode)in 12 (14.3%) cases,recurent bacterial pneumonia-9(10.6%),pneumocystis carinii pneumonia(PCP) 33(39,3%) cases, tuberculosis 27(32.2%),, divided in 23(27.4%) -cases as pulmonary tuberculosis and 4(4.8%) as generalised tuberculosis. Kaposy Syndrome- 2(2.4%),COPD -1(1.2%).cases. In the end of the study september 2015,13 patients died,12 of them had CD4 count level lower than CD4<199/ml. We found a positive correlations between ages and mortality (p=.003) ,the pattern of pulmonary complications with CD4+ count level.P<0.0001. **Conclusions:** In our study,the most common respiratory complications and with high mortality rate,are opportunistic infections from pneumocystis carinii pneumonia(PCP) and tuberculosis(TB).The level of CD4+ count is a useful indicator for developing respiratory infections and complications in HIV/AIDS patients.*

Keywords: CD4+,HIV/AIDS,TB,PCP,COPD

1. Introduction

In HIV-infected patients, it is usual the affection of the lungs; over 60% of patients have had at least one respiratory episode during the process of their disease. In early periods of HIV-infection, when the immune reaction is maintained relatively well, the model of respiratory infections is similar to the one noticed in the general population, but with a higher frequency. The risk of opportunistic infections and tumours is raised with the progression of the HIV-induced immunosuppression. During the last years, there have been some changes in the model of lungs diseases which are encountered in HIV-infected patients. These changes can be attributed to the wide availability and the administration of prophylaxis for pneumonia from *Pneumocystis Jirovecii* and the combined antiretroviral therapy (also known as highly active antiretroviral therapy or HAART). (1)

Especially, for patients with respiratory problems and advanced immune deficit, it is essential to consider all the differential diagnoses.

The CD4+ cell count is an excellent indicator of individual risk towards opportunistic infections of the patient. Over 200 cells/ml, typical opportunistic infections are less likely. In these patients, certain "usual" problems such as acute bronchitis and bacterial pneumonia can be anticipated. However, TB should always be noted. Even though the risk of immune deficit is increased, more than half of HIV + TB patients have more than 200 cells/ml (2, 3, 4).

In HIV-infected patients, the differential diagnosis of pulmonary diseases depends partially in the CD4+ cell count. When the CD4+ cell count is higher than 500/mm³, the patient might have bacterial pneumonia or TB, while the infection with opportune agents, such as *P. jirovecii*, CMV and *Aspergillus* is developed when the number of CD4+ cells is much lower. (5)

The CD4 cell count is an excellent indicator of the risk of developing an opportunistic infection or special neoplasm, apparently because the CD4 reflects the phase of the HIV disease and the degree of the immunodeficiency of the HIV-infected patient. Each of the respiratory diseases related to HIV, is usually developed in or under a characteristic level of CD4 cells and surprisingly or rarely it occurs over these levels. Respiratory diseases such as the infections of the upper respiratory tract, obstructive bronchial diseases, bacterial pneumonia, TB, non-Hodgkin's Lymphoma, pulmonary embolism and bronchogenic carcinoma, can occur in immunocompetent persons. Many of these diseases, however, are more usual in HIV-infected persons than in those who are immunocompetent. These diseases occur in the HIV-infected people in all cellular levels of CD4. With the decrease of the CD4 cell count, the incidence of many of these diseases increases. For example, there is a higher incidence of bacterial pneumonia in HIV-infected patients with a CD4 cell count <250 cells/mL, compared to patients with a CD4 count > 250 cells/mL. (6)

When the CD4 cell count falls under <500 cells/ml, the episodes of bacterial pneumonia can be recurrent and diseases from micro bacteria other than *M tuberculosis* can occur (e.g. *M kansasii*). (7, 8)

In a CD4 count of <200 cells/ml, bacterial pneumonia is often accompanied by the bacteraemia and sepsis, and the infection from *M tuberculosis* is often extrapulmonary or disseminated. Furthermore, PCP and pneumonia / *Cryptococcus neoformans*-caused pneumonia should be taken into consideration.

In a <100 cells / ml CD4 count, pathogenic bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and the pulmonary involvement from Kaposi Sarcoma or *Toxoplasma gondii* are diagnosed to be increased. (9)

In a CD4 cell count of <50 cells / ml, respiratory diseases caused by endemic fungi are developed (e.g. *Histoplasma capsulatum*, *Coccidioides immitis*), some viruses (mostly cytomegalovirus), Mycobacteria (*Mycobacterium avium* complex) and non-endemic mycoses (e.g. *Aspergillus* species). Often, these diseases are related to extrapulmonary or disseminated diseases, which dominate the clinical presentation. With exception of endemic fungal pathogens, the identification of these microorganisms in the sputum or bronchoalveolar lavage, can represent either a bronchial colonisation, or an actual pulmonary disease. In these cases, careful observation of the clinical situation and evaluation with invasive methods (e.g. lung biopsy) is very important prior to the beginning of treatment.

Since every opportunistic infection and neoplasia usually develops in or under a characteristic level of the CD4 cell count, knowing the CD4 cell count can be extraordinarily useful in defining possible diagnoses. For example, bacterial pneumonia (and probably TB, depending on the demography and region), but not the PCP should be highly considered for the differential diagnosis in an HIV-infected patient, the CD4 cell count of whom is obviously over 200 cells / mL. All these three pathologies, but not the pneumonia caused by endemic fungi or cytomegalovirus, should be considered for an HIV-infected patient, the CD4 cell count of whom is <200 cells / mL but also higher than 50 cells / mL. Lastly, most or all the diseases discussed above are diagnostic probabilities (even though some are more frequent than the others) in an HIV-infected patient, the CD4 cell count of whom is <50 cells / mL. In each of these examples, information regarding relative frequencies of the different infective causes and neoplasia within a certain range of the CD4 cell count is necessary for further processing of the differential diagnosis.

2. Materials and Methods

There is an observational retrospective study that has taken place in the year 2004-2015. The study was conducted in the University Hospital Centre “Mother Teresa” in Tirana, the Hospital of Infective Diseases. The study has included 77 (64 males and 13 females) patients with HIV/AIDS, 60 (77.9%) from the cities and 17 (22.1%) from the villages, who have experienced complications with pulmonary pathologies. The patients had an age range from 30 to 71 years old (average age 46.4±10.2) who were known to be diseased since 1 to 12 years (averagely 5.1 ±2.4) and with a medication period of 0.2 – 10 years (averagely 4.5±2.5 years). Until the termination of the medication, 13 (16.9%) patients have died. According to a protocol, demographic data and clinical-radiological features-CD4 counts have been extracted.

Statistical processing

All the collected data were put on Microsoft Excel, from which they were exported to SPSS (Statistical Package for Social Sciences) 20.0, with which the statistical data analyses were performed. The $p \leq 0.05$ values were considered significant.

3. Results

Related to age, there is no significant interconnection to the CD4+ level. An inverse correlation tendency is noticed, which is also related to the oldest age of the disease. No significant interconnection between sex and the CD4+ count ($P = 0.0918$) is noticed, but the majority of males – 49 (63.7%) are in a cell count less than 199 cells CD+/ml.

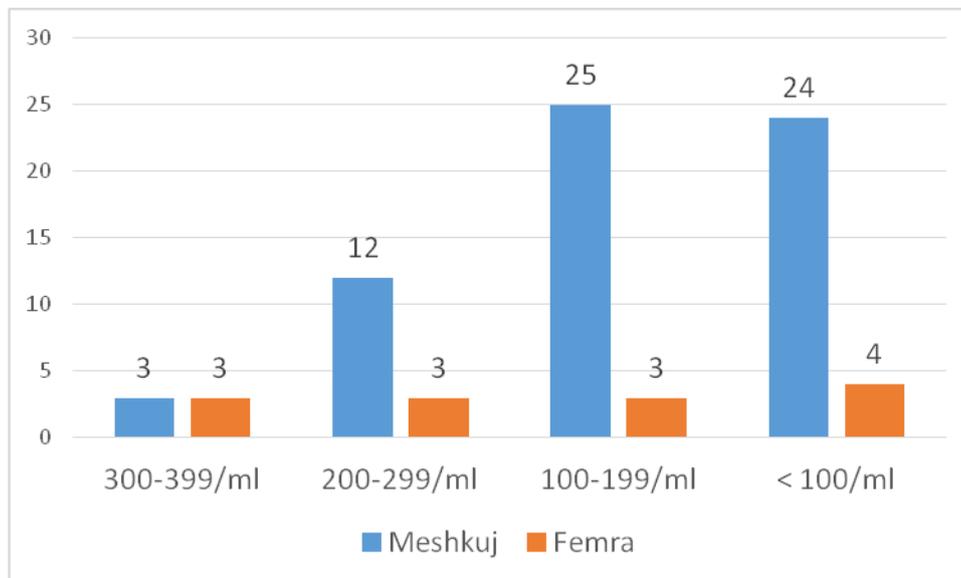


Figure 1: CD4+ cell count related to the gender of the HIV/AIDS-diseased people with pulmonary complications decrease of the number of CD4+, 24 (82.8% of the unemployed) with CD4 cells / ml under 199.

No significant correlation results between the profession and CD4+ level ($P = 0.4255$). In the unemployed people and workers there is an increase of the number of cases with the

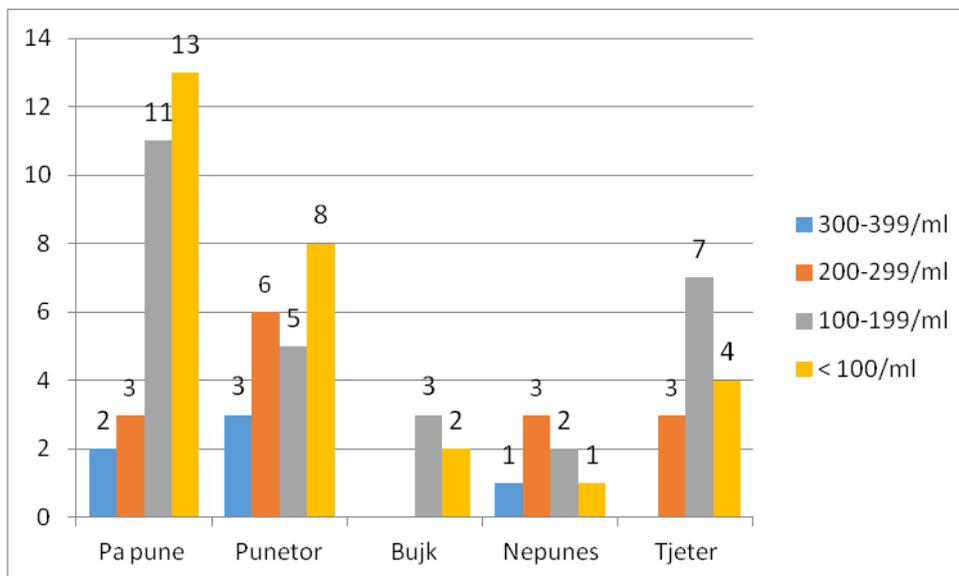


Figure 2: CD4+ cell count related to the profession of the HIV/AIDS-diseased people with pulmonary complications

There is a signification correlation related to the CD4+ cell count and the origin from the cities/villages ($P = 0.0309$), where 16 (94.1%) patients from the villages have a CD4 cell count under 199 cells/ml and 11 (64.7%) < 100/ml.

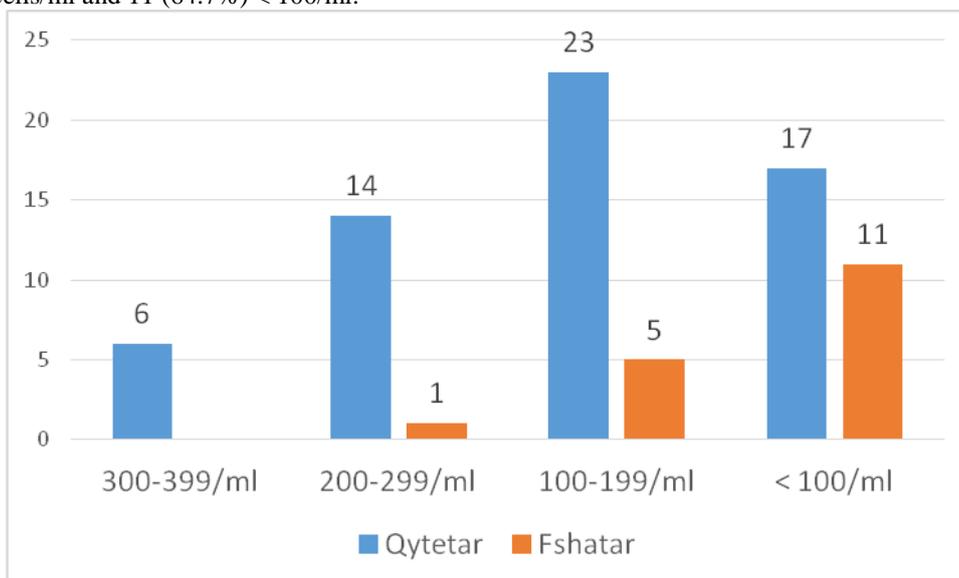


Figure 3: CD4+ cell count related to the origin of the HIV/AIDS-diseased people with pulmonary complications

In the persons with a secondary school education (8 years), there is an increase of the number of cases with the decrease of the CD4+ cell count (86% of them have a CD4 < 199/ml and 47.2% with a CD4 < 100/ml). This tendency is also present for those with a high school graduation (12 years).

In the patients who smoke, a decrease of the CD4+ cells is noticed with the increase of smoking quantity.

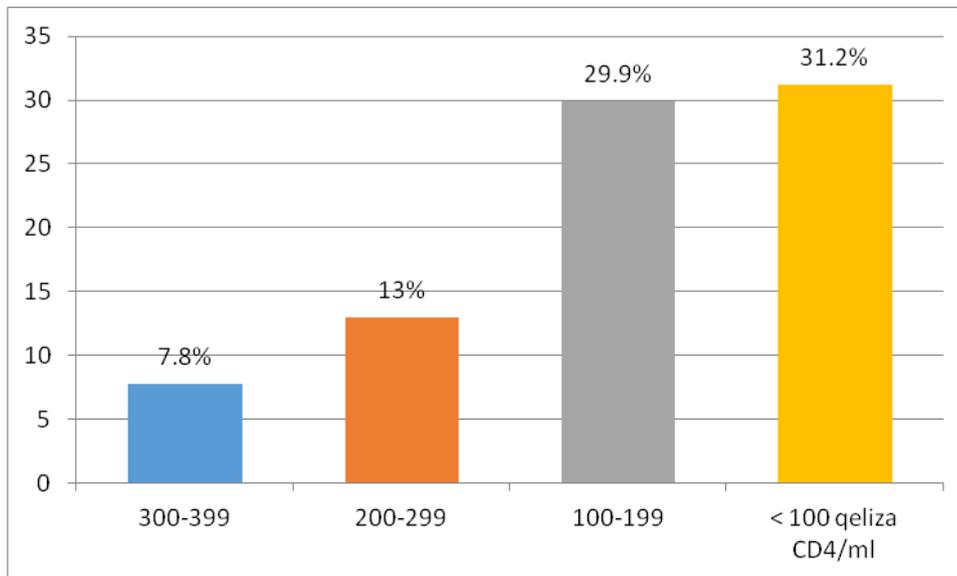


Figure 4: The CD4 cell count of patients who smoke (%)

No significant correlations have resulted between the CD4 count and route of infection ($P = 0.3136$), the medical structure where the diagnosis of HIV infection has been made, the period during which patients are known to be diseased, the manner of the beginning of the pulmonary disease. In the interconnection between clinical symptoms and the CD4+ cell count, a notable correlation with dyspnea when standing ($p = .027$) and chest pain ($p = .009$).

Furthermore, the appearing of mediastinal adenopathy occurs in a low level of CD4+ count and is better evidenced with the CT.

A strong correlation results between the type of pulmonary complication and the CD4+ cell count ($p < 0.0001$). Deaths have occurred in a CD4+ cell count under 199/ml.

Table 1: CD4+ cell count related to the pulmonary pathology of the HIV/AIDS-diseased people.

Pulmonary Complication		CD4 cell count				Total
		300-399/ml	200-299/ml	100-199/ml	< 100/ml	
Bacterial pneumonia (Case I)	Occurrences	6	6			12
	% from total	7.8%	7.8%			15.6%
Recurrent bacterial pneumonia	Occurrences		3	2	3	8
	% from total		3.9%	2.6%	3.9%	10.4%
Recurrent bacterial pneumonia PCP	Occurrences			1		1
	% from total			1.3%		1.3%
PCP	Occurrences			15	12	27
	% from total			19.5%	15.6%	35.1%
PCP Sarcoma Kaposi	Occurrences			2		2
	% from total			2.6%		2.6%
PCP Pulmonary TB	Occurrences			2	1	3
	% from total			2.6%	1.3%	3.9%
Pulmonary TB	Occurrences		5	6	8	19
	% from total		6.5%	7.8%	10.4%	24.7%
Pulmonary TB COPD	Occurrences		1			1
	% from total		1.3%			1.3%
Generalized TB	Occurrences				4	4
	% from total				5.2%	5.2%
Total	Occurrences	6	15	28	28	77
	% from total	7.8%	19.5%	36.4%	36.4%	100.0%

Pearson Chi-Square 74.922 Asymp. Sig. (2-sided) .000
 Likelihood Ratio 77.109 Asymp. Sig. (2-sided) .000
 Correlation coefficient 0.587, $p < 0.0001$

4. Discussion

From the study data it does result that there is a strong correlation between the type of pulmonary complication with the CD4+ cell count (Correlation of coefficient 0.587, $p < 0.0001$). A feature of the patients with immune deficiency

is their sensitivity against the infection from agents with little virulence. (10)

According to a study conducted by “The Centers for Disease Control and Prevention’s Adult and Adolescent Spectrum of HIV Disease Project”, (11) the major part (>80%) of bacterial pneumonias and pulmonary TBs have occurred in subjects with a CD4 number <400 cells / ml. Therefore, both these diseases should be considered in every CD4 count level, but are more usual when the cell count is <400 / ml.

However, the results in this group have shown that bacterial pneumonia (1,418 episodes; 8.4%) was a much more usual cause of pulmonary disease than TB (149 cases, 0.8%). On the contrary, most of the PCP cases have occurred in subjects with a CD4 cell count of <200 cells / ml (1,097 cases; 7.3%).

Knowing the CD4 cell count can be useful in narrowing down the field of differential diagnosis and knowing the relative frequencies of these pulmonary diseases can be useful in listing the possible diagnoses and making possible suggesting a diagnostic and therapeutic plan. For example, if a patient infected with HIV, shows respiratory symptoms and a CD4 cell count > 200 cells / ml, the PCP has few probability and bacterial pneumonia has more probability than TB. In this case, the diagnostic plan should include the sputum and hemoculture for the bacteria and the therapy should probably have usual bacterial pathogens as an objective.

With regards to age, there is no result of a significant interconnection with the CD4+ count. An inverse correlation tendency is noticed, which is also related to the older age of the disease. If natural aging in the HIV-negative persons leads to a long-term decrease in the immune system, including the CD4 cell count through the low degree of chronic immune activation / inflammation, then we can expect to see a bigger or earlier decrease of the CD4 cell count in the aged HIV-positive patients with the increase of the ART duration. The HIV infection in a long time, despite the viral inhibition by ART, is thought to speed up the natural trajectory of body aging, mainly due to the continuous immune activation and the induction of pro-inflammatory effects by ART, which lead to an early immunosenescence. It is not clear enough from these studies whether natural aging (calculated with time), along with the long-term inhibition of the HIV virus through the influence of long-term ART, affects the CD4 cell count trends or not. The authors suggest that the duration of ART and the age rise do not result in the decrease of the changes of the average CD4 cell count in a long-term period of the patients with virologic inhibition. The result is that the level of immune recovery achieved during the first 5 years of pre-treatment has remained for a long-term period. (12)

The actual viral load, in a much higher degree than any previous calculation, defines the progress of the norm of the CD4 cell count decrease. According to (13) "Age is related considerably to the change of viral load. A faster increase of the viral load is noticed in aged persons."

In the individuals who are not in antiretroviral treatment, the HIV infection usually includes a stable increase of the viral load, accompanied by a decrease in the CD4 cell level. If the HIV therapy has not begun, this leads to the development of opportune infections and AIDS-related deaths.

In the study, no significant interconnection between sex and CD4+ count is noticed. Even in the literature, generally, no correlation between gender, race or injected drug use and the increase of viral load is noticed. However, there have been certain data of an age-gender interaction ($p = 0.03$). The viral load increases with an average of 0.16 log₁₀ / copy /

ml every year in women aged 50 and over, as compared to an average increase of 0.11 log₁₀ / copy / ml in males of this age group. Age is an important factor ($p < 0.05$) in the decrease norm of CD4. Gender, race and injected drug use have not been related to CD4 decrease, and there is no evidence of interaction between these factors. (13)

There is no result of a correlation between profession and CD4+ count. For the unemployed and labour workers, there is an increase of the number of cases with the decrease of CD4+ count, which might be related to the lower level of demand for health services, lower health education and hard social-economic conditions.

There is a correlation between the CD4+ cell count and the city/village origin ($P = 0.03$), which is related to more unfavourable conditions in the demand and coverage of health services in the village, lower level of health education.

The study shows results that, in the persons with secondary education, there is an increase of the number of cases with the decrease of CD4+ cell count. The same tendency is in the ones with high school education, which is related to the same socio-cultural and economic factors mentioned above.

In smoker patients, a decrease of the CD4+ cell count with increased smoking quantity is noticed. Smoking stimulates local lung deficiency. It decreases the number of CD4 alveolar cells and the production of important pro-inflammatory cytokines (14) and inhibits the phagocytic capacity and alveolar macrophages (15).

No correlation between the infection route and CD4+ cell count has resulted. An increase of the CD4+ cell count cases resulted in heterosexuals with the decrease of the CD4+ cells count. According to the data for our country, almost three fourths of HIV diagnoses have been made in a late phase of the HIV infection with a CD4 cell count of less than 350, from almost half of them (47.1%) are present in a CD4 cell count of less than 200. This implies that a large part of people who live with HIV are likely not to be aware of their HIV infection and remain undiagnosed until they turn ill, or referral brings them to be tested. The late diagnosis is likely to be related to the high number of deaths, especially within the first year of diagnosis and later for HIV transmission. A cumulative total of 122 or 17.5% of deaths are reported in PLWHA; however, death reports might be underestimated. (16) Late diagnosis is also apparent from the study results – despite the health structure where the diagnosis of the HIV infection is made, the majority of cases is part of the categorizations with low CD4+ cell count.

No correlation results between the period when patients are known to be diseased and the CD4+ cell count, but the tendency of categorizing the cases leads towards those with lower CD4+ cell count, which is related to late finding. Furthermore, from the study results is not noticed any correlation between the manner of the beginning of the pulmonary disease and the CD4+ cell count, but a general characteristic of patients is noticeable, who are mostly with a lower cell count.

In the interrelation between the clinical symptoms and the CD4+ cell count, a meaningful correlation is indicated with dyspnea when standing ($p = .027$) and chest pain ($p = .009$). Furthermore, the appearing of mediastinal adenopathy occurs in a low CD4+ cell count and is better evidenced with the CT.

Respiratory symptoms are frequent complaints of HIV-infected individuals. This fact has its origins from "Pulmonary Complications of HIV Infection Study", a prospective observational study of a group of more than 1,150 HIV-infected subjects, conducted in more than 6 states in the United States of America. (17) The group of persons undergoing the study was similar to the structure of the AIDS cases reported in the United States from 1990 related to gender, race or ethnic background, as well as transmission categories of HIV. The subjects had a wide range of CD4 (<200 cells / ml: 19%; 200-499 cells / ml: 44% \geq 500 cells / ml: 37%). (17) The study showed that respiratory symptoms are a common complaint in HIV-infected individuals and are more and more frequent, when the CD4 count decreases to <200 cells / mL. The study subjects reported cough in 27%, dyspnea in 23%, and fever in 9% of the cases, in more than 12,000 clinical visits. These symptoms have been even more frequent in subjects with CD4 count <200 cells / ml in the time of visit or earlier. In this group of more than 4000 visits, subjects reported cough in 34%, dyspnea in 34% and fever in 17% of the cases. (17)

The results of a study were analysed in a centre of subjects infected and non-infected with HIV. (18) In this group, respiratory symptoms were significantly more frequent in the HIV-infected group than in the group without the HIV infection. These symptoms include dyspnea (41.6% vs 7.7%), cough (40% vs 25%), and sputum (41.9% vs 23.1%). The researchers found that actual or former smoking was the most important predictor of respiratory symptoms in the HIV-infected group.

From the 1221 screened teenagers, 1072 are studied; 60.1% were girls. The TB incidence degree was 16.32 per 100 PYO (person years observation) during the pre-antiretroviral therapy (pre-ART), but decreased to 2.25 per 100 PYO after the beginning of the ART. Advanced clinical stages, according to the WHO and the CD4 count <350 cells / ml provides TB incidence in the pre-ART group. The use of chemoprophylaxis with INH was accompanied by a considerable reduction of the TB incidence in the ART group, but not in the pre-ART group. (19)

As in the medicated persons, the general tendency of cases categorized in low CD4+ counts is followed in the ones who have not received regular medication. The same thing is apparent in the time of patients' medication. Results indicate that deaths occur in a CD4+ cell count under 199/ml.

5. Conclusions

The strongest indicator related to the type of pulmonary complication in HIV/AIDS patients results to be the number of CD4+ cells. Regarding the age, there is no significant interconnection with the CD4+ count, but an inverse correlation tendency is noticed, which is also related to the oldest age of the disease. A significant correlation has

resulted between the CD4+ cell count and the city/village origin, which is related to more unfavourable conditions in the demand and coverage of health service in the village, lower level of health education. Among the unemployed and labourers, the persons with secondary education, there is an increase of the number of cases with the decrease of the CD4+ cell count. It does result that deaths have occurred in a CD4+ cell count under 199/ml.

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