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HIV/AIDS AND OPPORTUNISTIC INFECTIONS
HIV/AIDS E AS INFECÇÕES OPORTUNISTAS
VIH/SIDA E INFECCIONES OPORTUNISTAS

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ABSTRACT

Objective: to investigate which infectious diseases most affect people living with HIV/AIDS and their relationship to the epidemiological and clinical profile of this population. **Method**: observational, longitudinal and retrospective research, developed at Hospital Rafael Fernandes in Mossoró/RN, Brazil. Twenty-two medical records of patients diagnosed with HIV/AIDS were used, and the collection took place between the years 2018 and 2019 with data from the last 5 years. **Results**: it was found that 59.09% were men over 40 years old (54.55%) and married (54.55%). A higher number reached people with elementary school education (55.56%), with a predominance of the occupations of farmer (23.81%) and housekeeper (14.29%). The main infectious diseases presented by the patients were cerebral toxoplasmosis (16.7%), HPV (13.3%), tuberculosis (13.3%) and gastroenteritis (13.3%). **Conclusion**: the study allowed the characterization of the epidemiological and clinical profile, as well as the identification of the main opportunistic infections. Such infections appeared with the aggravation of the clinical picture and were mainly associated with precarious living conditions, such as poverty, informal work, and low education levels. The interiorization of the epidemic was also observed, with dissemination of the infection towards small and medium-sized municipalities.

Descriptors: Acquired Immunodeficiency Syndrome; HIV; Opportunistic Infections; Health Profile; Clinical Evolution; Poverty.

RESUMO

Objetivo: investigar quais doenças infecciosas mais atingem as pessoas que vivem com HIV/AIDS e sua relação com o perfil epidemiológico e clínico dessa população. **Método**: pesquisa observacional, longitudinal e retrospectiva, desenvolvida no Hospital Rafael Fernandes em Mossoró/RN, Brasil. Utilizaram-se 22 prontuários de pacientes diagnosticados com HIV/AIDS, e a coleta se deu entre os anos de 2018 e 2019 com dados dos últimos 5 anos. **Resultados**: averiguou-se que 59,09% eram homens acima de 40 anos (54,55%) e casados (54,55%). Um maior número atingiu pessoas com Ensino Fundamental (55,56%), havendo predomínio das ocupações de agricultor (23.81%) e de

doméstica (14.29%). As principais doenças infecciosas apresentadas pelos pacientes foram toxoplasmose cerebral (16,7%), HPV (13,3%), tuberculose (13,3%) e gastroenterites (13,3%). **Conclusão**: o estudo possibilitou a caracterização do perfil epidemiológico e clínico, bem como a identificação das principais infecções oportunistas. Tais infecções surgiram com a piora do quadro clínico e apresentaram associação principalmente com as condições precárias de vida, como a pobreza, o trabalho informal e a baixa escolaridade. Constatou-se também a interiorização da epidemia, com disseminação da infecção em direção a municípios de pequeno e médio portes.
Descritores: Síndrome da Imunodeficiência Adquirida; HIV; Infecções Oportunistas; Perfil de Saúde; Evolução Clínica; Pobreza.

RESUMEN

Objetivo: investigar qué enfermedades infecciosas más afectan a las personas que viven con VIH / SIDA y su relación con el perfil epidemiológico y clínico de esta población. **Método:** investigación observacional, longitudinal y retrospectiva, desarrollada en el Hospital Rafael Fernandes de Mossoró/RN, Brasil. Se utilizaron 22 historias clínicas de pacientes diagnosticados con VIH/SIDA, y la recogida se realizó entre los años 2018 y 2019 con datos de los últimos 5 años. **Resultados:** se encontró que el 59,09% eran hombres mayores de 40 años (54,55%) y casados (54,55%). Un mayor número alcanzó a personas con Educación Primaria (55,56%), con predominio de ocupaciones de agricultor (23,81%) y domésticas (14,29%). Las principales enfermedades infecciosas que presentaron los pacientes fueron toxoplasmosis cerebral (16,7%), VPH (13,3%), tuberculosis (13,3%) y gastroenteritis (13,3%). **Conclusión:** el estudio permitió caracterizar el perfil epidemiológico y clínico, así como identificar las principales infecciones oportunistas. Tales infecciones surgieron con el empeoramiento de la condición clínica y se asociaron principalmente con las precarias condiciones de vida, como pobreza, trabajo informal y baja escoaridad. También se verificó la interiorización de la epidemia con la propagación de la infección hacia municipios pequeños y medianos.

Descriptores: Síndrome de Inmunodeficiencia Adquirida; VIH; Infecciones Oportunistas; Perfil Sanitario; Evolución Clínica; Pobreza.

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INTRODUCTION

The Acquired Immunodeficiency Syndrome (AIDS) corresponds to the most advanced stage of infection by the Human Immunodeficiency Virus (HIV), which has affinity for defense cells, causing immunosuppression of the immune system. With a slow progression and marked depletion of CD4+ T cells as main characteristics, its transmission happens through sexual, blood and vertical routes.[1]

Since the beginning of the epidemic, 74.9 million people worldwide have been infected with HIV; as for Brazil, 300,496 new cases were identified in the period between 2007 and June 2019, with 5,566 cases diagnosed in Rio Grande do Norte from 1980 to 2018; in Mossoró/RN, the municipality chosen for the research, 679 new HIV infections were detected from 2004 to 2018.[2-4]

Since its discovery, many changes have occurred in the epidemiological profile of those infected by HIV, including interiorization, with the disease spreading from large centers to municipalities in the interior, as well as a phase of impoverishment, reaching a greater number of people with low levels of education. The most affected population groups have also changed, with heterosexuals standing out and the increase in cases among women, characterizing the feminization of the epidemic.[5-6]

AIDS has been considered a chronic disease since the use of antiretroviral drugs and the susceptibility to the appearance of acute episodes due to factors such as non-adherence, failure or abandonment of treatment, which cause an increase in viral load and, consequently, a depletion of the immune system, favoring the appearance of opportunistic infections.[7-8]

Opportunistic diseases are infections that develop in the host organism when the immune system is weakened and its defense function is affected, which is an opportune moment for infections to develop.[9]

Considering that the progress of AIDS to a chronic condition disease has brought some repercussions, such as the decline of its being in evidence, the overlooking regarding the assistance to people living with HIV (PLHIV), and the systematization of the care, the defining of the theme for the research is appropriate, since it makes a rescue of the AIDS theme, identifying the infectious diseases that most affect PLHIV, as well as characterizing the clinical and epidemiological profile of these people.

The study has great relevance both for health services and for people living with HIV/AIDS, since it produces new data and new information that enable the creation of innovative strategies for coping, pointing out at the need for continuing education of professionals in relation to the change in the profile of the public, the main infections and their forms of prevention, as well as health education actions directed to PLHIV on these topics, aiming at health promotion and disease prevention.

In this context, the following research question was raised: what are the infectious diseases and how are they related to the epidemiological and clinical profile of people living with HIV/AIDS being treated in a reference hospital for infectious and parasitic diseases in the city of Mossoró/RN?

OBJECTIVE

To investigate which infectious diseases most affect the population living with HIV/AIDS and the relationship of these diseases with the epidemiological and clinical profile of these people.

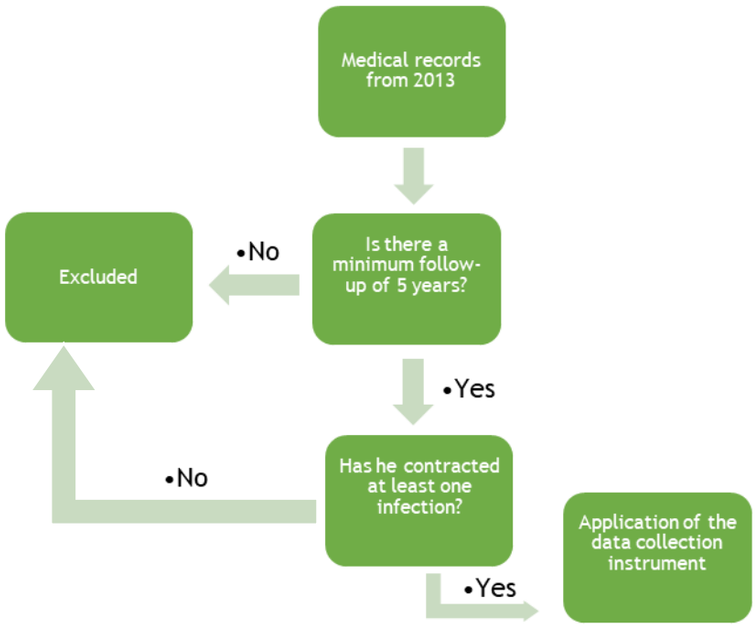
METHOD

This is an observational, longitudinal retrospective study with documentary analysis and quantitative approach, approved by the Research Ethics Committee of the Universidade do Estado do Rio Grande do Norte, under opinion number 2,852,813 and CAAE (Certificate of Ethical Appraisal Submission) 92432718.0.0000.5294, conducted at Hospital Rafael Fernandes (HRF) in Mossoró/RN, Brazil, specialized in infectious and parasitic diseases and reference in the treatment of AIDS for the western region of the state, which provides the Specialized Care Service (SCS) for the care of people living with HIV and viral hepatitis. This health unit currently cares for 1,188 patients from Mossoró and the surrounding region.

Data collection took place in primary data sources, with analysis of medical records between October 2018 and January 2019. All medical records opened from January to December 2013 were analyzed as they referred to patients monitored in the last 5 years by the mentioned health service, applying the data collection instrument previously developed by the researchers, based on the objectives of the study, to all medical records that presented at least one record of opportunistic infection in the period between opening the medical record and the last month of 2018.

The inclusion criteria were: patients who remained alive for at least 5 years (from 2013 to 2018), having presented at least one infectious-parasitic disease during that time. Medical records with the following characteristics were excluded: containing doubtful information, lacking the minimum necessary information, or any other problem that affected the credibility of the information; medical records of patients whose follow-up since their diagnosis in 2013 had been less than 5 years; and in cases of duplicate medical records, the one with the most information was chosen.

A total of 114 records were obtained by applying the inclusion and exclusion criteria in two stages: first, the records with a follow-up of less than 5 years were excluded, leaving 78 records in which the appearance of opportunistic infections was verified; then, the records in which the patients acquired at least one infection were included in the research, amounting to 22 records.



Flowchart 1 – Identification of medical records for data collection. Mossoró (RN), Brazil, 2019.

The data collection included the investigation of predictor variables such as age, sex, race, city of residence, marital status, profession/occupation, education, alcohol and tobacco use, date of diagnosis, viral load and CD4 cell quantification test results, as well as outcome variables such as the number of hospitalizations and the occurrence of opportunistic infections.

The database was built in EXCEL version 2017 format to make the descriptive tables; for the application of statistical tests, free statistical software R version 3.2.0 was used. In the quantitative variables evaluated in the study, descriptive statistics of measures, trends, and dispersion of the data were analyzed, such as minimum, maximum, mean, and standard deviation. For qualitative variables, descriptive analysis was performed by means of absolute and relative frequency distributions (%). For bivariate comparisons, the *Shapiro Wilk* and *Mann-Whitney* tests were applied, both with a 5% significance level.

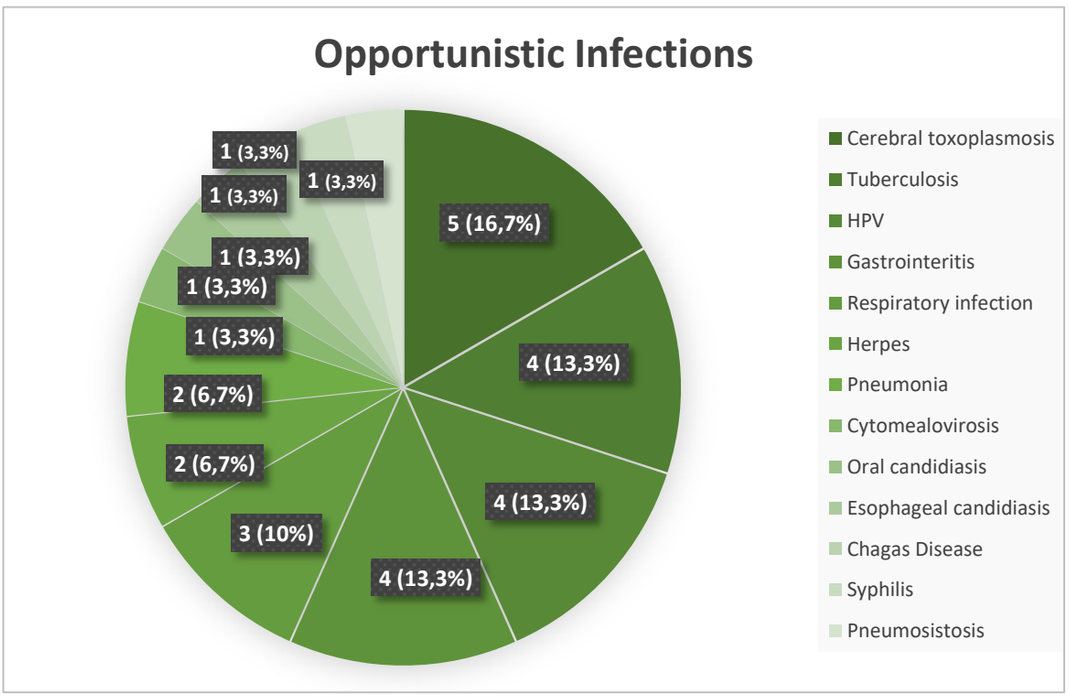
RESULTS

The study had a total of 22 medical records of patients diagnosed with HIV/AIDS in the year 2013, monitored until December 2018 in the HRF. 59.09% were identified as male and 40.91% as female, age range above 40 years old (54.55%) and married/stable union marital status (54.55%), 80.95% with children. Regarding the level of education, 55.56% had finished elementary school;

there was a predominance of farmers (23.81%) and housekeepers (14.29%). 61.90% did not use alcohol, and 63.16% denied smoking.

Race, marital status, partner's serology, having children, level of education, occupation, alcoholism or smoking were the most missing information in the medical records when analyzing only the data available.

The main infectious diseases presented by the patients were cerebral toxoplasmosis (16.7%), HPV (13.3%), tuberculosis (13.3%), and gastroenteritis (13.3%). This variable has multiple responses, i.e., different opportunistic infections were identified in the same patient, as well as the recurrence of diseases.



Graph 1. Frequency of opportunistic infections. Mossoró (RN), Brazil, 2019.

Some clinical variables are related to the results of CD4 cell count and viral load tests, performed every six months or according to evaluation and indication.

When comparing the main infectious diseases and the epidemiological profile of the patients, 5 people were observed to have acquired cerebral toxoplasmosis, most of them being female; younger than 40 years old; white; married/stable union; with elementary school education; with several professions/occupations, such as farmer, housekeeper, salesperson, merchant, and pensioner; in addition to not being a drinker or smoker.

As for the occurrence of tuberculosis, a frequency of 4 was achieved, with a predominance of males; aged within the two age groups (below and above 40 years); of white and brown races; married or single; illiterate; with profession/occupation of farmer, housekeeper, waiter, and pensioner; as well as drinkers and non-smokers.

HPV infection affected 4 people, mostly men; under 40 years old; white; single; illiterate or with elementary school education; with more repetition of the farming profession/occupation; as well as alcohol and tobacco users.

Regarding the occurrence of gastroenteritis, a frequency of 4 was identified, with equal distribution between both genders; predominance of the over forty-year-old group; white and brown races; married; illiterate; profession/occupation of farmer, housekeeper, fisherman, and factory worker; non-alcoholic, with an equal occurrence for those who use or do not use tobacco.

The association of infectious diseases with clinical variables has led to the understanding that people who contracted cerebral toxoplasmosis, tuberculosis, and gastroenteritis had lower CD4 cell values and higher viral load values. HPV infection occurred with different clinical conditions from the other diseases, appearing concomitantly with higher amounts of CD4 cells and lower viral load numbers.

Table 1. Clinical evaluations as compared to the infectious diseases. Mossoró (RN), Brazil, 2019.

Clinical evaluations as compared to the infectious diseases					
Variable	**Response**	**Cerebral Toxoplasmosis**	**Tuberculosis**	**HPV**	**Gastroenteritis**
Minumum CD4	**Yes**	17,00	17,00	228,00	2,00
	No	2,00	2,00	2,00	10,00
Maximum CD4	**Yes**	687,00	820,00	1.560,00	536,00
	No	1.560,00	1.560,00	988,00	1.560,00
Average CD4	**Yes**	337,42	328,41	618,26	238,43
	No	447,06	442,97	378,56	462,96
Minumum VL	**Yes**	44,00	156,00	61,00	66,00
	No	41,00	41,00	41,00	41,00
Maximum VL	**Yes**	1.456.462,00	1.216.638,00	59.021,00	1.068.609,00
	No	1.216.638,00	1.456.462,00	1.456.462,00	1.456.462,00
Average VL	**Yes**	288.907,44	238.406,39	14.180,42	134.375,19
	No	84.848,07	104.601,54	141.972,53	121.208,60

VL: Viral Load.

DISCUSSION

The epidemiological profile of PLHIV/AIDS has been undergoing transformations since its discovery, so that the constant changes have resulted in a profile characterized by feminization, heterosexualization, pauperization, interiorization, affecting a greater number of people with low levels of schooling. The results follow this process of transition in the characterization of infected people.[5,10]

The incidence of infection was most frequent in people over 40 years of age, diverging from the national panorama that indicates a higher number of cases among those between 25 and 39

years of age; thus, the study indicates the presence of adults who were diagnosed late, considering the evolution of the disease with the brief occurrence of opportunistic infections.[2]

The late diagnosis is usually associated with the absence of these people in health services, along with not requesting serology for HIV in routine appointments, since this conduct still has a focus on young people with greater vulnerabilities, such as drug users, sex workers, and men who have sex with men, despite the encouragement of public policies for periodic HIV testing in the population in general.[11-2]

In addition, older people exclude themselves from risks because they are convinced that HIV/AIDS is associated with young people, and they do not have adequate knowledge about the subject since they are excluded from activities that address sexuality and prevention of Sexually Transmitted Infections (STIs). Thus, the need for educational activities that enable the social deconstruction of this mistaken understanding involving this population in the context of risk behavior is recommended.[13]

Regarding race/color, there is a predominance of people who declare themselves white or brown, following the Brazilian scenario.[14-5] Regarding marital status, there is correspondence with the research carried out in Santa Cruz do Sul/RS, assuming that in these cases the contamination happens in extramarital relationships that result in transmission to partners.[16]

The profile of PLHIV is observed to have changed; however, educational actions have not taken this process into account, being carried out with intensity for the adolescent public and the LGBT+ population, failing to cover a majority that is part of the current profile: married individuals and not young adults who lack information on health promotion and prevention of diseases. Education can result in reduction of transmissibility, in greater adherence to treatment, and in better quality of life.[17-8]

The findings of this research point to a low level of education, which may be a factor for the delay in the identification of the disease and for the manifestation of opportunistic infections due to the fact that these people have little understanding about the transmission and prevention of HIV and other STIs, besides presenting behavioral practices that increase the risk of infection.[19-20]

Due to the low level of education, the data also show the predominance of jobs defined as informal, mostly self-employed, corroborating the study done in Passos/MG. The present research points out that the main occupations are farmers, housekeepers, fishermen and salespeople.[21] These occupations are characterized by unhealthy work processes and environments, with irregular working hours and unstable pay, resulting in the pauperization of the epidemic. Such factors, combined with the low income of this population, culminate in situations that generate negative im-

pacts on the treatment, such as the lack of a daily routine for taking the medications or attending medical appointments, in addition to enabling the occurrence of other diseases.[22-3]

The interiorization of AIDS was found in this research, and in works developed in Rio das Ostras/RJ and in Caxias/MA, showing that a large portion of the individuals live in municipalities adjacent to Mossoró, the city where the HFR is located.[6,24]

The existence of health professionals with the ability to recognize the peculiarities in the profile of PLHIV and adapt their actions to these specificities enables the implementation of activities consistent with reality, thus increasing the effectiveness and involvement in the treatment, promoting the achievement of a good clinical status, with satisfactory quality of life.[25-6]

The clinical status of PLHIV indicates the staging and evolution of the infection and should be monitored through regular medical appointments with the observation of some laboratory parameters, such as viral load and CD4 cell quantification tests, focusing on the investigation through anamnesis and physical examination of signs and symptoms that suggest opportunistic infections.[27]

The viral load quantification tests identify the number of copies of the virus existing in the body of the PLHIV, which results in a high number when there is absence, low adherence or resistance to treatment with antiretroviral drugs, becoming an important marker to identify the correct use and effectiveness of the treatment. The high results require greater attention in developing strategies for a proper adherence, such as creating a bond, more rigorous monitoring, providing health education, reducing the time between the request for tests and, if necessary, changing the therapeutic scheme.[28-30]

The increase in viral load as a consequence of abandonment, treatment failure, or resistance to treatment has as main outcomes the greater transmissibility of HIV, the increase of resistant strains and the quantitative and qualitative damage to the functioning of CD4 cells, causing suppression of the immune system in such a way that this clinical and laboratory state has great impact on public policies of care to PLHIV, representing threats to individual and collective therapeutic plans.[15]

The CD4 cell count makes it possible to analyze the condition of the immune system and, if performed on a regular basis, allows the development of strategies for the prevention of diseases.[31] There was an average of 422.14 cells/mm3 among the results, similar to studies that found figures above 350 cells/mm3, associating them with the use of antiretroviral drugs.[7,32]

CD4 cells and viral load have an inversely proportional relationship, since the increase in the number of virus copies in the body implies in the damage of CD4 cells, causing a reduction in their quantity. The immunosuppression caused by this relationship favors the development of opportunistic infections since there will not be enough cells to defend against the etiologic agent.[33]

In this study, the presence of the frequent opportunistic infections showed association of the clinical state with high viral load and drop in CD4 cells, as well as varied correlation about the epidemiological profile, so that these characteristics were also observed in another study.[34]

Cerebral toxoplasmosis was more incident in this study as the development of neurotoxoplasmosis triggers the manifestation of signs and symptoms, most commonly hemiparesis, headache, mental confusion, lethargy, and convulsion, resulting in major neurological sequelae, which may lead to death.[35]

Toxoplasmosis was contracted by women under 40 years old, white, married, with elementary school education, self-employed, and negatived regarding the use of licit drugs. A study developed in the city of Ponta Grossa identified similar aspects, in which users were observed to have little knowledge about the means of contamination and development of the disease, with a need for knowledge about preventive attitudes.[36]

Considering the means of transmission, guidance for PLHIV regarding the hygiene of the environment and food is relevant, focusing on raising awareness about the need to implement preventive conducts to these factors. However, the actions aimed at this public are still conducted based on approaches oriented to sexual aspects, not highlighting the importance of promoting the health of these people and the prevention of infections.[37-8]

The progression of cerebral toxoplasmosis showed a relationship with CD4 levels below 350 cells/mm3, reaching a minimum value of 60 cells/mm3 and a maximum viral load number of 1,456,462 copies/ml. These aspects were also identified in patients in Maceió/AL.[39]

Tuberculosis infection is characterized as an important disease for PLHIV, being linked to negative therapeutic outcomes with higher mortality. The most affected groups by this infection have living conditions that increase health risks, such as poverty, larger number of people in the same household, informal jobs, unstable income, use of alcohol and other drugs, as well as restricted access to information.[40-1]

Some of these conditions were identified in the study, such as alcoholism, low education level, low income, besides the predominance of males. This is justified by the fact that men do not have the habit of attending health services and generally do not have proper knowledge about infection and prevention. The use of alcohol, in addition to providing opportunities to attend crowded environments and favoring transmission, increases the rate of abandonment of the tuberculosis treatment.[42-3]

The mechanisms of action of HIV and Mycobacterium happen in a reciprocal way, reaching HIV-infected latent cells while promoting virus replication and decrease of CD4 cells. Consequently, the suppression of defense cells provides a favorable condition for its progression.[44]

A survey carried out in Fortaleza/CE showed that 53.1% of coinfected individuals had inadequate adherence to treatment due to difficulty in taking medications for both infections. The existence of coinfection and the absence of a treatment enhance the immune system involvement, resulting in an unfavorable prognosis.[45]

In the profile of people with gastroenteritis, there was a predominance of people over 40 years old, married, illiterate, and in informal jobs. Designated as a major socio-cultural and public health problem, with causing agents transmitted through water and food, besides being directly associated with the hygienization process,[46] gastroenteritis is linked to low socioeconomic and education levels, as well as to poor living conditions, with some of these conditions present in the findings. Regarding the clinical variables, a relationship was observed between low CD4 levels, high viral load levels, and the onset of gastroenteritis. The affected patients converge to a decline in their general condition, and may evolve to an advanced stage of malnutrition, dehydration, and death.[47-8]

The Human Papillomavirus (HPV) infection was also identified in the research as affecting young adult men. This phase of life and the use of illicit drugs are related to a greater number of partners, as well as low knowledge about the means of prevention of STIs, making them contributing factors to HPV infection.[49]

The occurrence of HPV infection in the present study saw a change in the pattern of clinical data from the previously discussed infections, since the development of HPV was found in periods of high CD4 cells with an average of 618 cells/mm3, while the viral load reached lower results, presenting a number of 14,180.42 copies/ml.

Considering these characteristics, a study was found only with HIV-positive women with HPV infection in the city of Montes Claros, in which they had CD4+ cell count above 500 cells/mm^3 and undetectable viral load; thus, the HPV infection showed no relationship with immunosuppression. This clinical state among PLHIV favors a greater amount of cure, as the evolution to more severe forms and the development of cancers are related to the depression of the immunological system.[50]

CONCLUSION

The study enabled the characterization of the epidemiological and clinical profile of PLHIV monitored at Hospital Rafael Fernandes, predominantly men over 40 years of age, with low education and engaged in informal jobs. In addition, it was found that these sociodemographic features were associated with the manifestation of the diseases. The main opportunistic infections were cerebral toxoplasmosis, tuberculosis, HPV and gastroenteritis, associated with the moments in which patients had lower CD4 cell counts and higher amounts of viral load, unlike HPV infection.

The analysis of this information allows us to identify that the manifestation of the diseases occurred with the aggravation of the patient's clinical condition, being mainly related to precarious living conditions such as poverty, informal employment and low education levels, so that such factors negatively affect the treatment, allowing the development of diseases. Given this context, the need to implement popular health education focused on the specificities of this group is recommended.

Some aspects can influence the monitoring of risk factors, such as the difficulty of connecting with some patients, since many live in other municipalities in the interior of the state, thus coming to the medical service only at pre-established times for appointments. Periodical exams and in situations of urgency and/or changes in the care situation occur in other health services without the proper counter-reference, adding to the lack of continuity of care in an interdisciplinary way by the different professionals working in the service, in view of the fact that the assistance and records are conducted in a fragmented and discontinuous way.

Another important factor concerns the prejudice and stigma that are attached to these individuals, leading many to hide their diagnosis even from family members, which can mean omission and, in some cases, changing the information given to health professionals during the care, which may diverge from the established profile and make it difficult to link patients to the services.

Among the limitations encountered during the research, it can be highlighted the lack of filling out of several fields on the first visit forms and on the patients' medical records, with no records of data obtained during the anamnesis or physical examination, in addition to the failure to run a large number of CD4 cell and viral load tests, restricting the verification of data on some variables.

The data found in the research provide the identification of the general condition and the main diseases that affect a number of patients living with HIV/AIDS, enabling the development of care and educational strategies by means of the health care professionals together with the users for the promotion of health and prevention of diseases.

Hence, some aspects need to be introduced and optimized in the clinical and educational practice of the nursing team and health service professionals, such as the development of training to better understand the most common types of infections in this population; conducting the nursing consultations through anamnesis and detailed physical examinations with an investigative look, paying attention to signs and symptoms of the diseases; adequate recording of medical appointments; active search for absent patients; periodic assessment of CD4 levels and viral load; supervision of treatment adherence; and the identification of the patients’ living conditions.

This paper allowed presenting an innovation in the scope of the research on this theme in the state of Rio Grande do Norte, since it could identify the opportunistic infections that most affect patients, highlighting the relationship of those people with their clinical and epidemiological profiles, as there are numerous studies on infections and profiles being investigated separately without establishing a relationship between these factors.

Further studies can be done for the prospective follow-up of this population, providing more data for more adequate care to the profile of the patient who uses this health service, with the possibility of extending to other services in order to make relevant comparisons to the care of people living with HIV/AIDS.

CONTRIBUTIONS

All authors contributed equally to the study design, data collection, analysis and discussion, as well as in the writing and critical review of the content with intellectual contribution and approval of the final version of the study.

CONFLICT OF INTERESTS

There are no conflicts of interests.

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