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PREDICTION OF CD4+ RANGES BASED ON THE TOTAL NUMBER OF LEUKOCYTES IN PEOPLE LIVING WITH HIV

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Objective. To predict the amount of CD4+/μL3 in sequences of patient records with CD4 T lymphocyte values above 500 cells/μL3 and / or between 200 to 500 cells/μL3 from the absolute leukocyte count in the context of the theory of probability.
Materials and methods. Two mathematical inductions were performed to find predictive mathematical relationships for CD4+/μL3 when they are above 500 cells/μL3 and between 200 to 500 cells/μL3, from the absolute count of leukocytes. Subsequently, the probability of success of the predictions was calculated, two blind studies were performed on 80 remaining data, and sensitivity and specificity were calculated for both cases.
Results and discussion. If there are more than three records in time per patient, and these are above 500 CD4/μL3 cells or between 200 to 500 CD4/μL3 cells, finding that the absolute leukocyte count has a greater or equal value to three and lower to 4 for all the records, the following record will be maintained with a measurement of CD4 lymphocytes>500 or between [200, 500], if in the absolute count of leukocytes of the patient sequences a value of four is observed and CD4+ ranges from 200 to 500 cells/μL3, it can be deduced that there will be at least one measurement of CD4 +>500 cells/μL3 associated with a leukocyte measurement / μL3 greater than 3.7.
Conclusions. We established two temporal mathematical patterns capable of predicting the CD4+/μL3 count from the absolute leukocyte count.

Keywords: leukocytes, CD4 T lymphocytes, blood count, HIV, antiretrovirals

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ПРОГНОЗИРОВАНИЕ ДИАПАЗОНОВ CD4+ НА ОСНОВЕ ОБЩЕГО КОЛИЧЕСТВА ЛЕЙКОЦИТОВ У ЛЮДЕЙ, ЖИВУЩИХ С ВИЧ

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Цель. Определить количество CD4+ на мкл^3 в последовательностях историй болезни пациентов со значениями CD4 Т-лимфоцитов выше 500 клеток/мкл^3 и/или от 200 до 500 клеток/мкл^3 на основе абсолютного количества лейкоцитов в контексте теории вероятности.
Материалы и методы. Были выполнены две математические индукции, чтобы найти математические предсказания для CD4+ на мкл^3, когда они превышают 500 клеток/мкл^3 и от 200 до 500 клеток/мкл^3 от абсолютного количества лейкоцитов. Впоследствии была рассчитана вероятность успеха прогнозов, были проведены два слепых исследования на 80 оставшихся данных, и для обоих случаев были рассчитаны чувствительность и специфичность.

Результаты и их обсуждение. Если имеется более трех записей на одного пациента и они содержат более 500 клеток CD4+ на мкл^3 или от 200 до 500 клеток CD4+ на мкл^3, обнаруживается, что абсолютное количество лейкоцитов больше или равно 3 и ниже 4 для всех записей, следующая запись будет поддерживаться с измерением лимфоцитов CD4>500 или между [200, 500], если в абсолютном подсчете лейкоцитов последовательностей пациентов наблюдается значение 4 и CD4+ колеблется от 200 до 500 клеток/мкл^3, можно сделать вывод, что будет по крайней мере одно измерение CD4+ >500 клеток/мкл^3, связанное с измерением лейкоцитов на мкл^3 больше 3,7.

Заключение. Установлены две временные математические модели, позволяющие прогнозировать количество CD4+ на мкл^3 по абсолютному количеству лейкоцитов.

Ключевые слова: лейкоциты, CD4+ Т-лимфоциты, ВИЧ, анализ крови, антиретровирусные препараты

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Introduction. Different studies developed by United Nations (UNAIDS) Reveal that about 36 million people live with HIV [1]. Besides, until 2017 more than 78 million people have been infected by HIV in more than 40 million have died [2]. The diagnosis of HIV represents the first step in the cascade of elements necessary to an appropriate treatment and following up. Among the different treatments designed to manage HIV patients is anti-retroviral therapy which is useful to achieve maximal suppression of HIV replication, helping to increase the immune response [3]. One of the elements used to make surveillance of patient please through the measurement of CD4+ lymphocytes [4].

Considering the previous statements, the necessity of obtaining differently strategies that allow to establish the trajectory of CD4+ cells from the diagnosis to the surveillance during antiretroviral treatment has arose [5–7]. In The medical literature, different clinical and descriptive studies have documented the temporal changes in the trajectory of CD4+ cells count after initiating anti-retroviral treatment [5–11]. However, these kinds of methodologies might not be easy to develop, so other strategies that include lineal effects [7–9] have been implemented, but the correlation of these results with the real trajectory of CD4+ counts in some cases do not match [7].

The theory of probability is tightly bound to set theory, through axioms formulated under the notions of belonging and not belonging of set theory [12]. For example, the possible events how far to determine experiment are grouped in a sample space, similar to the way that elements are grouped in a set. In the current literature, some studies have been developed with basis on these theories, showing their capability of predicting CD4+ counts through values of leukocytes and lymphocytes counts from the complete blood count [13–18].

Continuing this line of investigation, the purpose of this study is to design a methodology based on the theory of probability, capable of obtaining predictions in time of the number of CD4+ cells when these values are found simultaneously in two mathematical relationships. The first one accounts for CD4+ >500 cell/μL3 while the second scenario is for counts that are between 200 and 500 cells/μL3, considering the absolute leukocyte count to obtain predictions. These relations are studied from different registries along time from flow cytometry and complete blood count values of patients that have initiated antiretroviral treatment.

Materials and methods. *Definitions.*

Range 1: [CD4+ >500] cells/μL3 and the absolute leukocyte count, corresponding to CD4+ >500 cells/μL3, associated to one absolute leukocyte count.

Range 2: [200< CD4+ < 500] cells/μL3 and the absolute leukocyte count, corresponds to the CD4+ counts whose values are found only within the values 200 and 500 cells/μL3, associated to an absolute leukocyte count.

$$P(A) = \frac{R\ range\ repetitions}{Totality\ of\ repetitions\ of\ the\ ranges} = \frac{N_R}{N}\ Equation\ 1$$

Probability of the ranges of [CD4+/μL3 >500] and [200< CD4+/μL3< 500 cells/μL3]: frequency of occurrence of the distribution of leukocytes in CD4+ counts >500 and between 200 to 500 cells/μL3 over the totality of repetitions of these two ranges.

Population. The registries of flow cytometry and blood count of 91 HIV-positive patients were taken along time, whose leukocytes were associated to CD4+ counts that varied in one or two ranges (see definitions). At the moment of selecting patients, variables such as sex, age, time elapsed between sampling and antiretroviral regimens were not considered. The information of the registries used in this study was gathered between 2016 and 2019 by Servicios y Asesorías en Infectología and evaluated by an expert specialist in infectious diseases.

Procedure. Two mathematical inductions were developed. The first one used 6 cases denominated prototypes (P1 to P6) which were selected by having more than two CD4+ and leukocyte counts in different times, meeting the conditions of the first range (see definitions). The second induction was conducted with 5 cases, also prototypical (Q1 to Q5) which also has more than two registries along time and meet the conditions of the second range (see definitions). With the 80 remaining samples, 35 were used to confirm the first mathematical induction and 45 to confirm the second induction through two blind studies.

All these calculations were conducted in a software developed for this investigation in C++

Diagnostic tests. Two diagnostic tests were performed to evaluate the reproducibility and clinical applicability of the diagnostic criteria of the prototypes chosen for both mathematical inductions. For that, the values of CD4+ counts were unmasked in order to calculate false positives, true positives, false negatives and true negative.

Ethical considerations. This investigation fulfills the technical, scientific and administrative standards for investigation in health, stipulated in the legal resolution No. 8430 of 1993 of Colombia and, specifically, with the title 11, which refers to investigation with human beings. It belongs to the category of investigation without risk given that mathematical calculations are performed over results of medically prescribed diagnostic tests, not affecting diagnostics or treatments of patients and honoring their integrity and anonymity.

Results and discussion. The number of samples analyzed for CD4+ counts that are found in the ranges 1 and 2 (see definitions) in which the 6 and 5 prototypes used for the inductions, respectively, can be observed in table 1. The counts of CD4+ for the six prototypes in range 1 varied between 517 and 1359 cells/μL3 and the absolute leukocyte counts varied between 5.3 and 12.1 cells/μL3. The counts of CD4+ for the five prototypes in range 2 varied between 517 and 1359 cells/μL3 and the absolute leukocyte counts varied between 5.3 and 12.1 cells/μL3.

In total, 215 registries corresponding to 50 patients were analyzed whose registries were divided in two ranges. The first one for CD4+>500 cells/μL3 and the second for counts between [200–500] cells/μL3. For the first range, 19 patients had 1 registry, 11 patients had 2 registries, 13 patients had 3 registries, 6 patients had 4 registries and 1 patient had 5 registries. For the second range, 21 patients had 1 registry, 14 patients had 2 registries, 7 patients had 3 registries, 4 patients had 4 registries and 4 patients had 5 registries.

Carryover effect for absolute leukocyte counts found in ranges 1 and 2.

From the analysis of these two mathematical inductions, two mathematical conditions were established for subsequent cases that present at least two registries for CD4+ and absolute leukocytes counts fir a same patient in the ranges 1 and 2, which can be presented individually or with both conditions. The conditions are as follows:

When taking more than three registries in time of a same patient and the leukocytes counts are >3000 mm^3, then in orders of magnitude, the variable will remain close to that value in the remaining registries.

If in the leukocyte count a value greater than 4000 is observed and the CD4+ count varied in a range of [200, 500], it can be deduced that at least one of the measurements of CD4+ will be greater than 500 cells/μL3 associated to leukocyte counts greater than 3.700 mm^3, which is formally known as carryover effect.

The application of the first condition can be observed in the case 9. The first registry dated on 18/11/16 with an absolute leukocyte count of 3.400 with a CD4+ count >500 cells/μL3, from 15/06/17 until 22/06/2018 the absolute leukocyte counts in orders of magnitude are close to 3 in most cases and where in a range of [200, 500] cells/μL3. The dynamics of leukocytes and CD4+ lymphocytes can be observed in figures.

The second condition can be observed in patients 1, 5, 29, 30 and 35 of table 3, where all the absolute

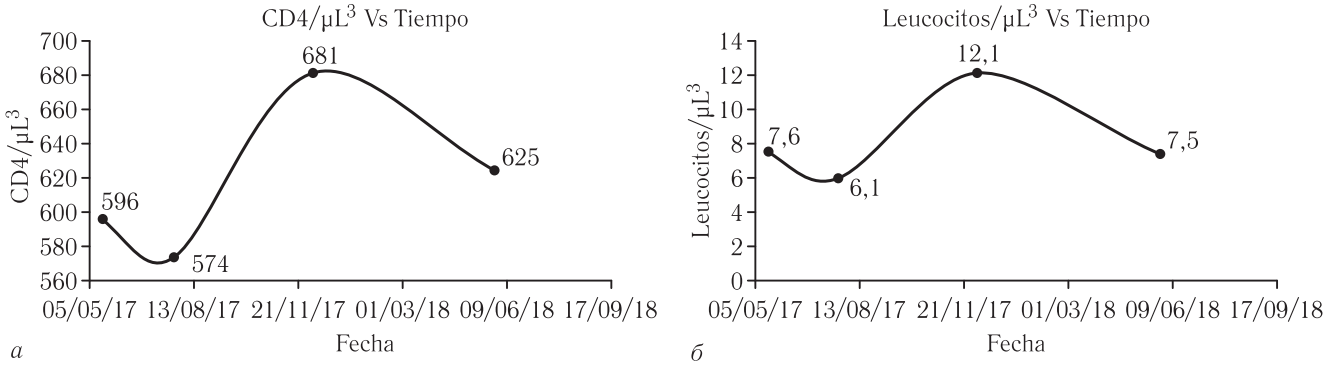

Figure. Dynamics for the prototype P1 in time for a) CD4+ counts in the ranges >500 cells/μL3 and b) absolute leukocyte counts
Рисунок. Динамика для прототипа P1 во времени для *а* — количества CD4+ в диапазоне >500 клеток/мкл^3 и *б* — абсолютного количества лейкоцитов

leukocyte counts are higher than 4 when these are in the range [200, 500] cells/μL3 and in the range CD4+ >500 those values are higher than 3.7 (see table 4).

Conclusion. This is the first study where mathematical inductions from which mathematical predictive parameters are established through relations between CD4+ cell counts within the ranges of 500 cells or between [200< CD4+ < 500] cells/μL3 and the absolute leukocyte counts in HIV-positive patients after initiating antiretroviral therapy in the context of the theory of probability. Besides, the term «carryover effect" was established in order to be applicable to two ranges established for this study. This effect for a leukocyte count is a way to understand how the system will behave after finding the leukocyte count in a value of 3.700 cells in a range >500 cells/μL3. The application of this methodology will contribute with more precise following ups of patients in time during their treatment with antiretrovirals and to avoid opportunistic infections, in order to augment their overall survival.

The results of this study reveal that the establishment of a pattern between the behavior of CD4+ and leukocytes counts along time are more important than any other analysis focused in CD4+ counts in view that the results suggest that the dynamics behaviors, although apparently fluctuating, in fact present patterns between both variables. Future studies will be performed with CD4+ counts in ranges <200 cells/μL3, as well as the possible combinations that can be arranged between the different ranges.

The way of observing mathematical relations of the individual values of leukocytes and lymphocytes to predict CD4+ cells was previously developed in a study designed with two methodologies based on set and probability theories. In the context of set theory, a mathematical order was established for the behavior of leukocyte populations with respect to lymphocytes and CD4+ counts that were represented based on set theory, from the belonging or not to four defined sets [13]. In the context of probability, the achieved results of the first methodology were refined, establishing ranges of leukocytes that fulfill the specific characteristics of belonging to any of the four sets and probability was applied to each of them, which allows to quantify how the established sets behave in the induction [14]. The reproducibility and clinical applicability of both methodologies was confirmed in subsequent studies [15, 16], finding a higher refinement of the predictions in the moment that both methodologies were unified [17, 18].

This new line of investigation shows the possibility of developing studies that apply methodologies that are available to patients with low-income. This is possible in view that only two variables are taken in time and predictions can be calculated by only requiring a complete blood count. Moreover, the effectivity of the antiretroviral regimens in time can also be evaluated in this line, limiting the variables to consider by specialists in infectious diseases in order to establish the trajectories of CD4+ counts after antiretroviral treatment, which at present time has not been established in conventional clinical studies [5–7].

The development of other predictive methodologies has contributed to successfully contribute in other areas of medicine such as in adult and neonatal cardiology [19, 20] achieving the first predictions of mortality [20]. Other predictive methodologies have been developed to predict the number people infected by malaria [21] and people living with HIV/AIDS [24].

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