

TEMPORAL PREDICTION OF THE BEHAVIOR BETWEEN THE NUMBER OF LEUKOCYTES AND CD4+ T LYMPHOCYTES IN HIV POSITIVE PATIENTS WITH ANTIRETROVIRAL THERAPY

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Abstract

Introduction: *the elevated cost of flow cytometry for the following up of CD4+ T lymphocyte counts has justified the search for predictive methodologies of this values that contribute to simplify and reduce costs of the therapeutic management of patients with HIV/AIDS.* **Objective:** *to establish the possible predictive mathematical correspondences between the CD4+ count > 500 cells/ μL^3 from the amount of leukocytes/ μL^3 .* **Methodology:** *a mathematical induction was carried out with eight samples in time to establish a predictive pattern between the leukocyte count in a count of CD4+ > 500 cells/ μL^3 . The validation of the predictive pattern was confirmed in 62 samples that had CD4+ counts previously masked. Then, the probability of success of the pattern was established as well as sensitivity and specificity.* **Results:** *the mathematical pattern of the eight samples revealed that, for a CD4+ count > 500 cells/ μL^3 , a value greater than 3.7 leukocytes/ μL^3 is presented, with a value of one when calculating the probability and, of 100% when calculating the sensitivity and specificity.* **Conclusions:** *the present study revealed a deterministic mathematical order from which it is possible to establish direct correspondences between leukocyte count leukocytes/ μL^3 greater than 3.7 and CD4+ greater than 500 cells/ μL^3 in the context of probability theory.*

Keywords: CD4 +, HIV, antiretroviral, flow cytometry, leukocytes.

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Predicción temporal del comportamiento entre la cantidad de leucocitos y linfocitos T CD4+ en pacientes VIH positivos con terapia antirretroviral

Resumen

Introducción: El elevado costo de la citometría de flujo para el seguimiento de los valores de CD4+ en pacientes con VIH ha justificado la búsqueda de metodologías predictivas de este valor, que contribuyan a simplificar y reducir los costos del seguimiento terapéutico de los pacientes con el VIH/SIDA. **Objetivo:** establecer las posibles correspondencias matemáticas predictivas entre el recuento de CD4+ > 500 células/ μL^3 y la cantidad de leucocitos/ μL^3 . **Metodología:** se realizó una inducción matemática con muestras en el tiempo de ocho pacientes, para establecer un patrón predictivo entre el recuento de leucocitos presentes en un recuento de CD4+ > 500 células/ μL^3 . La validez del patrón predictivo fue confirmada en 62 muestras a las cuales les fue previamente enmascarado el recuento de CD4+/ μL^3 . Posteriormente fue calculada la probabilidad de acierto del patrón establecido, así como la sensibilidad y especificidad. **Resultados:** el patrón matemático de las ocho muestras reveló que, para un recuento de CD4+ > 500 células/ μL^3 , se presenta un valor mayor de 3.7 leucocitos/ μL^3 , con valor de 1 al calcular la probabilidad y, del 100% al calcular la sensibilidad y especificidad en la muestra restante. **Conclusiones:** el presente estudio reveló un orden matemático determinista a partir del cual es posible establecer correspondencias directas entre el recuento de leucocitos leucocitos/ μL^3 mayores a 3.7 y CD4+ mayores a 500 células/ μL^3 en el contexto de la teoría de la probabilidad.

Palabras clave: CD4+, VIH, antirretroviral, cuadro hemático, citómetro de flujo, leucocitos.

Introduction

Acquired Immunodeficiency Syndrome (AIDS) is a consequence of a primary and initial infection by the Human Immunodeficiency Virus (HIV) that progresses due to an immunosuppression mechanism produced by the retrovirus, this pathogen classically affects T cells of immune response and macrophages, cells characterized for being first responders to primoinfection, in conjunction with dendritic presenting antigen cells and lymph nodes [1]. This entity has been established as the pandemic of transmissible nature with greater consequences to diverse populations since the XX century [2]. According to The Joint United Nations Programme on HIV/AIDS (UNAIDS) and

World Health Organization (WHO) data, since the initial reported cases from the early eighties and until the end of 2020 around 85 to 90 million people have been infected and between 40 to 44 million people have died due to collateral infectious diseases caused by AIDS, which is the terminal stage of HIV infection (HIV / AIDS) [3].

The HIV diagnosis represents a first step in treatment cascade and a necessary element to initiate prevention strategies [4]. Nowadays there are tests which possess high sensitivity and specificity, known as gold standard, such as flow cytometry, to measure current status of HIV infection by analyzing CD4 + lymphocytes count present in the patient. However, the high costs of personnel and equipment make it a

non-accessible test to the general population. Many countries have no guaranteed access to this type of technology due to these costs [5]. The WHO guidelines [6,7] state that a total lymphocyte count $<1,200/\text{mm}^3$ is necessary to direct the initiation of antiretroviral treatment for individuals who do not have a report of CD4 + lymphocyte count and who are symptomatic because of HIV, and although the total lymphocyte count is a useful tool, WHO continues emphasizing the need to have the number of CD4 + to start treatment and have control over it [6,7].

Probability theory allows to quantify the changeable behavior of an event in time and to establish the possible occurrence of it [8]. The development of methodologies based on the probability theory in medicine, has allowed to develop a methodology that establishes a mathematical order to predict the CD4 + T lymphocyte count, from the analysis of the behavior of the leukocytes and lymphocytes measured in complete blood count [9]. Based on this last study, we proposed the development of a methodology able to predict the CD4+ count $>500 \text{ cells}/\mu\text{L}^3$ from the amount of leukocytes/ μL^3 in time, in context of probability theory, whose predictive value can be verified in different samples taken for the same patient.

Methods

Definitions

Correspondence between the range greater than 500 CD4+/ μL^3 and leukocytes/ μL^3 : We analyzed the correspondence between CD4+/ μL^3 greater than 500 and the amount of leukocytes/ μL^3 of eight samples which were called prototypes, by means of a mathematical induction whose results were considered as a diagnostic comparison pattern.

Likelihood of range: frequency of appearance of the distribution of leukocytes/ μL^3 present in a CD4+ count $> 500 \text{ cells}/\mu\text{L}^3$, over the total of repetitions of a range, represented in equation 1.

$$P(A) = \frac{\text{Repetitions of r range}}{\text{Total of repetitions of ranges}} = \frac{N_R}{N} \text{ Equation 1}$$

Equation 1. Where:

P(A): Likelihood of range.

N_R : Repetitions of r range.

N: Total of repetitions of ranges.

Population

The flow cytometry and blood count record with CD4+ counts $> 500 \text{ cells}/\mu\text{L}^3$ were recorded over time for 70 HIV patients receiving any antiretroviral therapy, simultaneously leukocyte count/ μL^3 were taken. In the present study, the age and sex of the patients was not considered, as well as the type of treatment. The database reviewed for this study was collected between 2016 and 2019 by Servicios y Asesorías en Infectología (SAI) company, these records were duly evaluated by the company's expert professional.

Flow cytometry and blood count recording were recorded for 70 HIV-positive patients with CD4 + counts $> 500 \text{ cells}/\mu\text{L}^3$ who during the course of the study were receiving antiretroviral therapy with the following drug combinations:

1. Emtricitabina (FTC), Dolutegravir (DTG) + Abacavir (ABC)
2. Lamivudina (3TC), Raltegravir (RAL) + Tenofovir Disoproxil Fumarato (TDF)
3. Emtricitabina (FTC) y Raltegravir (RAL) + Abacavir (ABC)*

The leukocyte count/ μL^3 was taken simultaneously. The age and sex of the patients, as well as the type of treatment, were not taken into account in the present study. The database reviewed for this study was collected between 2016 and 2019 by the company Servicios y Asesorías en Infectología (SAI), these records were duly evaluated by the company's expert professional.

Procedures

The correspondence between the CD4+/ μL^3 range greater than 500 and the leukocyte

count/ μL^3 was established by a mathematical induction from the 70 patient records, 8 patients prototypes were selected whose mathematical characteristics are representative of the behavior of this sample range. In this way we established the amount of leukocytes/ μL^3 on which predictions can be made over time of the CD4+ count greater than 500 cells/ μL^3 . To confirm the result of induction in the remaining 62 patients, a blind study was carried out to validate the methodology, for which a C ++ code software was designed in which the probability of presentation of the established mathematical pattern was also calculated.

Statistical analysis

A blind study was carried out to evaluate the reproducibility of the methodology, for which the CD4+/ μL^3 count, taken on different days of the remaining 62 patients were masked to calculate false positives, true positives, false negatives, and true negatives by means of a 2x2 contingency table, determining the specificity and sensitivity of the present methodology compared to conventional clinical evaluation.

Ethical considerations

The present study complies with technical, scientific and administrative standards for health research, established in resolution No. 008430 of 1993 in title 11 for human research. According to this resolution the study is in risk-free category, in view of the fact that the methodology was applied in registries product of paraclinical exams that have been prescribed medically, without modifying the diagnosis or management of the patients and preserving the integrity and privacy of these [10,11].

Results

A total of 276 records (medical examinations containing CD4+ cell and T leukocyte counts on different dates for each of the patients) corresponding to 70 patients were evaluated, in which 3 patients presented 1 record, 6 patients

presented 2 records, 13 patients presented 3 records, 24 patients presented 4 records, 18 patients presented 5 records, 6 patients presented 6 records (see table 1). Table 2 shows representative values of total number of patients selected for the study. Additionally, the table shows the difference in days on which the CD4+ count > 500 cells/ μL^3 and leukocytes/ μL^3 were recorded, for the 70 patients. The results of the mathematical induction established from the 8 prototypes revealed that for a population whose CD4+ count > 500 cells/ μL^3 , the amount of leukocytes/ μL^3 is greater than 3.7. These predictions were subsequently confirmed in the remaining 62 patients analyzed.

To observe the trajectory of the CD4+ count > 500 cells/ μL^3 and the amount of leukocytes/ μL^3 , counted on the same day for the same patient, these values were represented on a coordinate plane, where the y-axis contains the counting values of CD4+ > 500 cells/ μL^3 and the leukocyte count/ μL^3 , and the x-axis the time in years (See figures 1, 2 and 3). These figures make possible to visualize that regardless of the shape of the CD4+ of > 500 cells/ μL^3 count trajectory, the amount of leukocytes will not be less than 3.7, thus establishing a measurement pattern for T CD4+/ μL^3 lymphocytes when these they are greater than 500 cells/ μL^3 from a fixed value of 3.7 leukocytes/ μL^3 .

To observe how the methodology works, the time stamp of patient 39 was taken, which has the highest number of records, with a total of 6 records. On the first date 08/25/16 a count of 4.9 leukocytes/ μL^3 and a CD4+ count of 775 cells/ μL^3 was counted. From the second record made on 20/02/17, it was observed that the amount of leukocytes/ μL^3 was greater than 3.7 and the CD4+ count > 500 cells/ μL^3 , indicating so far that the diagnostic parameter established in the induction is applicable in the second exam. When analyzing the other records of patient number 39, it can be observed that no record has a CD4+ count <500 cells/ μL^3 and a value less than 3.7 leukocytes/ μL^3 (see table 2).

In an analogous way, we proceeded to analyze the records of the 62 remaining patients.

Finally, the probability calculation generates a result of one for the leukocyte value of 3.7 or

greater in a CD4 + count > 500 cells/ μL^3 . Diagnostic confirmation between the mathematical predictions and the conventional clinical procedure yielded values of sensitivity and specificity of 100%.

Table 1. Number of records and patients representative of the total number of samples selected for the study, the records represent the populations of the CD4+ count > 500 cells/ μL^3 and the amount of leukocytes/ μL^3 present in this amount of CD4+ T lymphocytes.

No	Records by patient								
1	4	15	5	29	5	43	4	57	3
2	2	16	2	30	5	44	2	58	3
3	4	17	5	31	4	45	3	59	1
4	3	18	5	32	6	46	5	60	1
5	3	19	5	33	4	47	4	61	6
6	1	20	4	34	5	48	2	62	4
7	4	21	3	35	5	49	3	63	4
8	4	22	4	36	4	50	5	64	3
9	4	23	3	37	4	51	4	65	3
10	5	24	6	38	6	52	4	66	5
11	3	25	4	39	6	53	2	67	4
12	2	26	3	40	5	54	4	68	3
13	5	27	4	41	5	55	4	69	6
14	5	28	4	42	4	56	5	70	5

Source: self made

Table 2. Representative values of the total number of patients in Table 1, in which the number of records for the same patient can be observed together with the dates of registration, in addition to the populations of the CD4+ count > 500 cells/ μL^3 and the number of leukocytes/ μL^3 , posted for each of these dates.

No.	Date	CD 4+/ μL^3	Leukocytes/ μL^3	No.	Date	CD 4+/ μL^3	Leukocytes/ μL^3
24	07/23/16	767	5.5	39	08/25/16	775	4.9
	12/12/16	698	9.7		02/020/17	811	5.4
	05/25/17	844	9.9		08/03/17	748	5.6
	11/25/17	624	6.5		03/05/18	714	4.8
	06/27/18	666	6.6		08/16/18	673	3.7
	09/17/18	1203	6.4		02/13/19	676	5
	07/06/16	664	6		61	07/30/16	1038
12/17/16	1359	9.7	02/06/17	993		6.6	
06/06/17	863	8	09/08/17	945		5.5	
01/09/18	609	5.3	04/02/18	863		7.1	
07/11/18	702	5.8	09/18/18	868		6.4	
01/09/19	705	6	03/06/19	933		7.7	
38	06/13/16	666	5.6	69		08/26/16	806
	03/03/17	660	5		01/26/17	842	7.3
	09/23/17	839	5.2		07/07/17	641	6.3
	03/24/18	612	5.9		01/09/18	658	6.3
	08/31/18	733	4.5		08/02/18	700	5
	01/19/19	632	4.6		02/20/19	646	5.4

Source: self made

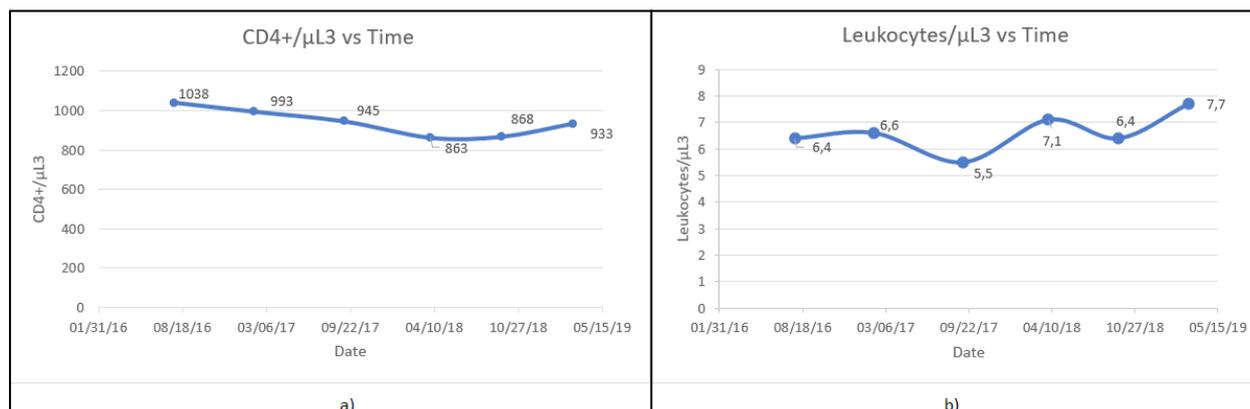


Figure 1. Dynamics in time for a) the CD4+ count > 500 cells/ μL^3 and b) the leukocyte count/ μL^3 for patient No. 32 of table No. 2.

Figure 2. Dynamics in time for a) the CD4+ count > 500 cells/ μL^3 and b) the leukocyte count/ μL^3 for patient No. 61 of table No. 2.

Source: self made

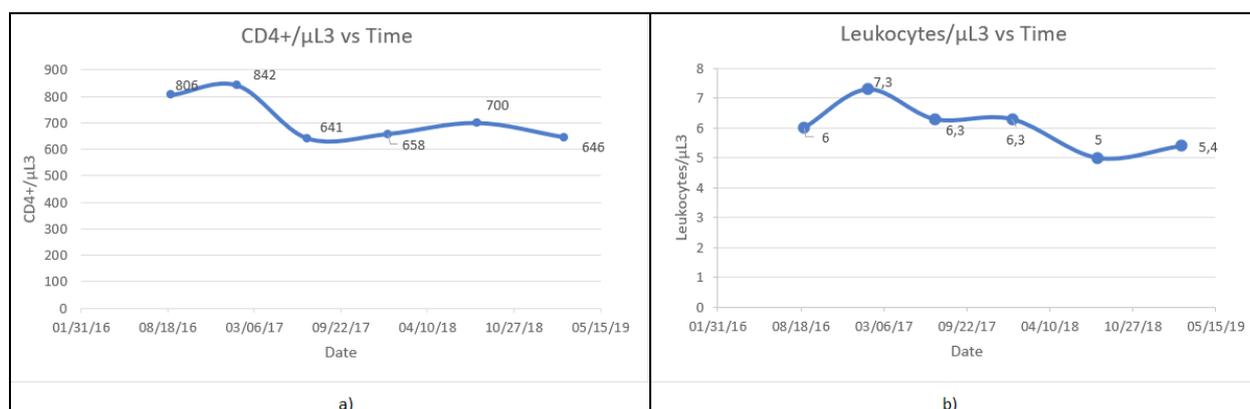


Figure 3. Dynamics in time for a) the CD4+ count > 500 cells/ μL^3 and b) the leukocyte count/ μL^3 for patient No. 69 of table No. 2.

Source: self made

Discussion

This is the first work that develops a mathematical induction to establish a mathematical correspondence between the amount of leukocytes/ μL^3 and CD4+/ μL^3 recorded in the complete blood count and flow cytometry, which could be used to predict the CD4+ count greater than 500 cells/ μL^3 in the context of probability theory. Mathematical induction revealed that the value greater than or equal to 3.7 leukocytes/ μL^3 was present in the remaining 62 patients whose CD4+ count was greater than

500 cells/ μL^3 . As described in the results with an example of the application of the methodology, the diagnostic parameter established in the present study can be applied independently of the patient's age, sex, CD4 + counts, hemoglobin, viral load, etc.

The results of the present methodology contribute directly to patients who, due to their income, cannot perform a flow cytometry after starting their treatment with antiretrovirals, and who can instead perform a complete blood count which shows an absolute leukocyte

count and that is more accessible in any health context. In such contexts, this methodology would have a great impact on follow-up of these patients improving their quality of life. The methodology established the mathematical parameter for the range greater than 500 CD4 +/ μL^3 . A future study is going to analyze the behavior of leukocytes when they are in a range of less than 500 CD4 +/ μL^3 .

Previously, a predictive methodology was developed from the theory of sets and probability theory to obtain CD4+ T lymphocyte values from 8 established ranges with absolute values of leukocytes and lymphocytes, generating triples with these three variables, which were analyzed according to the operations of the sets. By doing this, it was observed that those leukocyte ranges of 4000 and 5000 cells allow obtaining predictions for CD4+ counts lower than 570 cells with 100% success and 90% respectively, with confirmations in studies of up to 800 cases [12]. More recently, a redefinition of some sets was generated to evaluate ranges of less than 4,000 cells with probability values of 1 [13], which confers a greater specificity to perform clinical follow-ups of patients on antiretroviral management.

The mathematical induction developed from probability theory demonstrate the prediction capacity of the methodology, besides that it provides an acausal vision to the analysis of this phenomenon, as modern theoretical physics does with the approach of problems of nature. In this way, the dynamics of CD4 + counts are conceived in an objective manner, independent

of patient risk factors, clinical history, age and other diagnostic tests, which in the long run complicate the analysis of this phenomenon and which have not provided many answers from the point of view of conventional clinics studies [14-21]

This theoretical conception of nature problems in medicine has allowed the design of cardiology studies to evaluate and differentiate geometrically normal cases from the abnormal ones from the point of view of fractal geometry and dynamic systems. It has also made possible the obtention of mortality prediction in the intensive care unit [22], to characterize normal and abnormal behaviors in cardiac dynamics by means of values of proportions of entropy [23], temporal prediction of the number of persons infected by malaria [24], the binding of peptides to HLA class II [25] and cellular morphometry in cervical cancer [26].

Conclusion

A mathematical pattern was found between leukocyte count and CD4+ cell count in HIV patients, suggesting that the phenomenon is practically deterministic, and the applicability of the developed methodology for predictions in patient follow-up.

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References

1. Abbas A, Lichtman A, Pillai S *Inmunología Celular y Molecular*. 9 Edición. Madrid: McGraw Hill; 2018. p. 478
2. Castilla J, Sobrino P, Lorenzo JM, et al. Situación Actual y Perspectivas Futuras de La Epidemia de VIH y Sida En España. Vol 29. Gobierno de Navarra, Departamento de Salud; 2006.
3. De Cock K, Jaffe H, Curran J. Reflections on 40 Years of AIDS. *Emerging Infectious Diseases*. 2021;27(6):1553-1560.
4. Morales-Miranda S, Loya-Montiel I, Ritter J, et al. Factors associated with HIV testing among men who have sex with men in Guatemala City. *Int J STD AIDS*. 2019;30(6):577-585.
5. Zijenah LS, Katzenstein DA, Nathoo KJ, et al. T lymphocytes among HIV-infected and -uninfected infants: CD4/CD8 ratio as a potential tool in diagnosis of infection in infants under the age of 2 years. *J Transl Med*. 2005;3(1):6.
6. WHO, UNAIDS. Joint United Nations Programme on HIV/ AIDS. Progress on global access to antiretroviral therapy: an update on “3 by 5”. Vol. 2005
7. WHO, UNAIDS. Joint United Nations Programme on HIV/ AIDS. Epidemic update 2005.
8. Gnedenko B, Khintchine, A. *Introducción a la teoría de las probabilidades*. Barcelona: Montaner y Simon. 1968.
9. Rodríguez J, Prieto S, Bernal P, et al. Predicción de la concentración de linfocitos T CD4 en sangre periférica con base en la teoría de la probabilidad. Aplicación clínica en poblaciones de leucocitos, linfocitos y CD4 de pacientes con VIH. *Infectio*. 2012;16(1):15-22.
10. Ministerio de Salud. Resolución Número 8430 de 1993. Bogotá, Colombia [Internet]. 1993 [consultado el 26 May 2019]. Disponible en: <https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/RESOLUCION-8430-DE-1993.PDF>
11. Asociación Médica Mundial. Declaración de Helsinki. Fortaleza, Brasil [Internet]. 2013 [consultado el 26 May 2019]. Disponible en: <http://www.isciii.es/ISCIII/es/contenidos/fd-investigacion/fd-evaluacion/fd-evaluacion-etica-investigacion/Declaracion-Helsinki-2013-Esp.pdf>.
12. Rodríguez J, Prieto S, Correa C, Mora J, Bravo J, Soracipa Y, et al. Predictions of CD4 lymphocytes' count in HIV patients from complete blood count. *BMC Medical Physics*. 2013; 13(1).
13. Rodríguez J, Prieto S, Correa C, Forero M, Pérez C, Soracipa Y, et al. Teoría de conjuntos aplicada al recuento de linfocitos y leucocitos: predicción de linfocitos T CD4 de pacientes con virus de la inmunodeficiencia humana/sida. *Inmunología*. 2013; 32(2): 50-56.
14. Means AR, Risher KA, Ujeneza EL, Maposa I, Nondi J, Bellan SE. Impact of Age and Sex on CD4+ Cell Count Trajectories following Treatment Initiation: An Analysis of the Tanzanian HIV Treatment Database [published correction appears in *PLoS One*. 2017 Jan 6;12 (1):e0170155]. *PLoS One*. 2016;11(10):e0164148. Published 2016 Oct 7. doi:10.1371/journal.pone.0164148.
15. Obirikorang C, Quaye L, Acheampong I. Total lymphocyte count as a surrogate marker for CD4 count in resource-limited settings. *BMC Infect Dis*. 2012;12:128. Published 2012 Jun 7. doi:10.1186/1471-2334-12-128.
16. Napoli, Anthony M., et al. “Absolute Lymphocyte Count in the Emergency Department Predicts a Low CD4 Count in Admitted HIV-positive Patients.”
17. Chen J, Li W, Huang X, et al. Evaluating total lymphocyte count as a surrogate marker for CD4 cell count in the management of HIV-infected patients in resource-limited settings: a study from China. *PLoS One*. 2013;8(7):e69704. Published 2013 Jul 18. doi:10.1371/journal.pone.0069704
18. Lok JJ, Bosch RJ, Benson CA, et al. Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. *AIDS*. 2010;24(12):1867–1876.
19. Rodríguez, Javier, Carlos Pérez, and Ribká Soracipa. «Predictive ranges for the population of CD4+ lymphocytes for HIV positive patients on antiretroviral treatment.» (2022).
20. Li, Bei, et al. «A novel prediction model to evaluate the probability of CD4+/CD8+ cell ratio restoration in HIV-infected individuals.» *AIDS* 36.6 (2022): 795-804.
21. Hughes RA, May MT, Taylor N, et al. Long terms trends in CD4+ cell counts, CD8+ cell counts, and the CD4+:CD8+ ratio. *AIDS* 2018; 32: 1361-1367.
22. Rodríguez J. Dynamical systems applied to dynamic variables of patients from the Intensive Care Unit (ICU). Physical and mathematical Mortality predictions on ICU. *J. Med. Med. Sci*. 2015; 6(8): 102-108.

23. Rodríguez J, Prieto S, Ramírez L. A novel heart rate attractor for the prediction of cardiovascular disease. *Informatics in medicine*. 2019; 15(100174):1-9.
24. Javier R, Prieto S, Correa C, Pérez C, Soracipa M. Dinámica de la epidemia de malaria en Colombia: predicción probabilística temporal. *Rev. Salud pública*. 2017;91(1):52-59.
25. Rodríguez J, Bernal P, Prieto P, Correa C, Álvarez L, Pinilla L, et al. Predicción de unión de péptidos de *Plasmodium falciparum* al HLA clase II. Probabilidad, combinatoria y entropía aplicadas a las proteínas MSP-5 y MSP-6. *Archivos de alergia e inmunología clínica*. 2013; 44(1): 7-14.
26. Rodríguez J, Prieto S, Correa C, Dominguez D, Cardona DM, Melo M. Geometrical nuclear diagnosis and total paths of cervix cell evolution from normality to cancer. *J Can Res Ther* 2015; 11(1): 98-104.

