Mathematical temporal prediction of CD4+ lymphocytes in HIV/AIDS patients in antiretroviral treatment

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Research

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Abstract

Background: The measurement of CD4 + lymphocyte count through flow cytometry, is necessary for the following up of HIV-infected patients in antiretroviral therapy, however, populations in low-income countries are limited to this test. For this, values of leukocytes and CD4 + lymphocytes counts greater than 500, between 200 and 500 and lesser than 200 cells were taken from 250 HIV-infected individuals in sequential dates up to three years. Then, temporal series of 12 prototypical patients were analyzed in search of predictive patterns between CD4 + lymphocytes and leukocytes, and then, these patterns were applied with the remaining data in a blind study in order to calculate the probability of success of the methodology for each range and its combinations, as well as sensitivity and specificity values.

Results: Five patterns with predictive percentages greater than 99% were found for the distinct conditions of the methodology, with sensitivity and specificity values of 99%.

Conclusions: A predictive theoretical simplification was achieved between leukocytes counts and CD4 + lymphocytes. This method could be useful to improve the surveillance and survival of HIV-infected individuals in low-income countries where flow cytometry cannot be afforded.

Background

It has been estimated that there are more than 36.9 million people living with the Human Immunodeficiency Virus (HIV) and that the deaths due to HIV or the Acquired immunodeficiency Syndrome (AIDS) are greater than 35 million since the appearance of HIV. For 2017, it was calculated that the deaths due to HIV were 940.000 [1]. The incidence of the disease has augmented, especially in Africa, Middle East, Eastern Europe and Central Asia, so this epidemic remains as a public health global problem, which makes necessary to obtain advances in this field to reduce the mortality of the population, especially in infants [2].

The CD4 + count, obtained through flow cytometry, is useful to observe the progression of HIV in individuals infected and its one of the cornerstones to initiate antiretroviral management. However, flow cytometry is not a worldwide available test, particularly in low-income countries, given the limitation of the high costs associated [3]. The anterior, has generated the study of surrogate markers [4, 5] and the development of methodologies that predict CD4 + lymphocytes count [6–8].

Some of these models have implemented machine learning techniques that predict CD4 + counts changes. These models sometimes also include parameters such as the viral load, hemoglobin, age, among others, with which predictions with accuracies greater than 80% [8] and specificities of 96% have been obtained [9]. Nevertheless, these methods have a limited application and require further testing.

Based on probability theory and algebra of sets, a methodology was developed to predict the value of CD4 + lymphocytes considering specific populations of total leukocytes and lymphocytes, achieving predictions with a probability of one [10, 11]. The predictive capability of this methodology has been confirmed with its application to datasets of 500 and 800 patients, obtaining precisions of 90% and 100% to predict CD4 + counts lesser than 570 cells/ μL^3 when total leukocytes values are 5000 and 400 leukocytes, respectively.

The purpose of this investigation is the development of a novel clinically applicable methodology applicable for HIV-infected individuals in antiretroviral management that allows to predict the population of CD4+/μL^3 in ranges: greater than 500 cells, between 200 and 500 cells, lesser than 200 cells and its combinations with respect to the absolute leukocyte count. The development of this method would allow to conduct temporal predictions of this marker in low-income countries in the absence of flow cytometry.

Methods

Population

For this study, values of CD4 + flow cytometry and complete blood count registries from 250 patients were taken from a database compiled by “Servicios y Asesorías en Infectología”. This database was evaluated by an expert infectious diseases specialist. Data was taken from each individual in different dates with an average difference of 6 months. This was necessary to generate a temporal sequence of registries for all the inviduals.

The variables that were found in the registries of the patients were: absolute counts of leukocytes, metamyelocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and reactive lymphocytes; erythrocyte sedimentation rate, mean platelet value; red blood count; scattergram; percentage of lymphocytes, leukocytes, metamyelocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and reactive lymphocytes; platelet distribution width; mean corpuscular volume; prolymphocytes; mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; red blood cell distribution width; blast cells; promyelocytes; myelocytes; serology (RPR), RNA, HIV-1, viral load (log10); absolute counts and percentages of TCD3+, TCD4 + and TCD8 + lymphocytes; CD4+/CD8 + ratio and total lymphocytes.

Procedure

Given that this methodology is based on the method of theoretical physics [12] in which the observation of phenomena is simplified and abstracted, the studied phenomenon was simplified to only two variables that allowed to established essential mathematical predictive relationships, choosing for this absolute counts of leukocytes and CD4 + cells. Then, an inductive process was conducted to develop the mathematical predictive patterns based on the temporal behavior of the sequence of registries of 12 individuals that had a characteristic representative behavior. This induction allowed to establish a predictive evaluation of CD4 + lymphocytes from absolute counts of leukocytes. From this, 5 groups of possible dynamics were established as follows:

1. Dynamics in which all the registries of the sequences present values of CD4 + lymphocytes > 500 cells/μL^3.
2. Dynamics in which all the registries of the sequences present values of CD4 + lymphocytes between [200,500] cells/μL^3.
3. Dynamics in which all the registries of the sequences present values of CD4 + lymphocytes lesser than 200 cells/μL^3.
4. Dynamics in which the registries of the sequences present values of CD4 + lymphocytes > 500 cells/μL^3 but also between [200,500] cells/μL^3.
5. Dynamics in which the registries of the sequences present values of CD4 + lymphocytes < 200 cells/μL^3 but also between [200,500] cells/μL^3.

Afterwards, considering these groups, the mathematical predictive patterns found were applied to develop a software in C + + to automatize the predictive procedure. It is worth nothing that the theory of probability was applied to calculate the possibility of predictive accuracy in the totality of patients, which means that this theory is the one that allows to obtain predictions about the phenomenon studied, such as in quantum physics [12].

Ethical aspects

According to the scientific, technical and administrative regulations for investigation in health, stipulated in the Resolution 8430 of 1993, especially in the title 11, concerning to investigation with human beings, this investigation is classified in the category of no risk since mathematical analysis are conducted over clinical practice test results previously prescribed, not affecting the patients in any therapeutic or diagnostic aspects. Also, this investigation is based on the ethical principles for investigation that involucrate human beings of the World Medical Association's Declaration of Helsinki, the Nuremberg Code, and the Belmont Report, respecting the integrity and anonymity of patients.

Statistical analysis

A blind study was performed where the values of the variables of the remaining cases not used in the induction process were blinded. Then, after the mathematical induction was developed, the values of CD4+/μL^3 were then unblinded to calculate false positive and negatives as well as true positive and negatives through a contingency table to calculate sensitivity and specificity. This procedure allowed to statistically confirm the precision of the method, but this does not allow to obtain predictions.

Results

In total, 1022 registries corresponding to 250 patients were analyzed, for which 91 patients presented 1 registry, 63 patients presented 2 registries, 65 patients presented 3 registries, 77 patients presented 4 registries, 46 patients presented 5 registries and 12 patients presented 6 registries. An example of the variables considered and analyzed for each patient are displayed in Table 1.

Table 1
Sequential values of the variables reported for case No. 42.

Days elapsed		203	202	226	245
Date	14/09/2016	5/04/2017	24/10/2017	7/06/2018	7/02/2019
$CD4^+$ lymphocyte count	1102	1197	1429	742	1012
Eosinophils count	0.07	0.12	0.13	0.07	0.19
Eosinophils (%)	1.3	1.8	1.8	1.2	2.5
Red blood cell distribution width	11.2	10.7	12.3	10.2	12.4
Platelet distribution width	15.3	18.3	17.5	16.5	14.3
Basophils count	0.01	0.04	0.03	0.02	0.05
Basophils (%)	0.2	0.6	0.4	0.4	0.7
Blast cells	NI	NI	NI	NI	NI
Mean corpuscular hemoglobin concentration	33.4	33.5	33.6	34.1	34.8
Scattergram	NI	NI	NI	NI	NI
Erythrocytes count	5.39	5.70	5.37	5.48	5.11
Erythrocyte sedimentation rate	8	10	8	3	13
Mean corpuscular hemoglobin	34.0	32.3	32.5	31.3	32.4
Lymphocytes count	2.26	2.63	3.43	2.61	2.80
Lymphocytes (%)	40.7	38.7	47.6	45.3	36.7
$CD3^+$ lymphocyte (%)	76.93	81.89	75.75	85.39	76.93
$CD4^+$ lymphocyte (%)	38.33	42.29	38.77	45.59	37.02
$CD8^+$ lymphocyte (%)	36.53	39.54	34.12	37.35	38.98
Reactive lymphocyte counts	0.07	0.13	0.11	0.14	0.14
Reactive lymphocyte (%)	1.2	1.9	1.6	2.4	1.8
$CD3^+$ lymphocyte count	2212	2319	2792	1389	2104
$CD8^+$ lymphocyte count	1050	1120	1258	608	1066
Total lymphocyte count	2875	2832	3686	1660	2735
Viral load (log_{10})	< 1.6	< 1.6	< 1.6	< 1.6	1.75
Metamyelocytes count	NI	NI	NI	NI	NI
Myelocytes count	NI	NI	NI	NI	NI
Monocytes count	0.48	0.49	0.60	0.50	0.70
Monocytes (%)	8.6	7.2	8.3	8.7	9.2
Plateletcrit	0.203	0.257	0.161	0.249	0.227

NI: no information

Days elapsed		203	202	226	245
Prolymphocytes count	NI	NI	NI	NI	NI
Promyelocytes count	NI	NI	NI	NI	NI
Absolute leukocyte count	5.6	6.8	7.2	5.8	7.6
$CD4^+/CD8^+$ ratio	1.05	1.07	1.14	1.22	0.95
HIV-1 RNA	< 40	< 40	< 40	< 40	56
Neutrophils count	2.74	3.51	3.02	2.56	3.88
Neutrophils (%)	49.2	51.7	41.9	44.4	50.9
Serology (RPR)	Non-reactive	Reactive 1 dilution	Reactive 2 dilutions	Reactive 4 dilutions	Reactive 16 dilutions
Mean corpuscular volume	102	96	97	92	93
Mean platelet volume	7.90	9.70	8.30	9.10	7.80
NI: no information					

The minimal and maximal values for CD4 + counts oscillated between 34 and 1,429 while the values of absolute counts of leukocytes oscillated between 2.2 and 12.9 (Table 2). Examples of the dynamics of leukocytes and lymphocytes are exhibited in Figs. 1 to 4.

Table 2
Values of CD4 + lymphocytes and leukocytes of the most representative cases of the analyzed sample.

Case		$CD4^+$ (cells/μL^3)	Leukocytes (cells/mm^3)
234	min.	34	4.7
	max.	358	6
245	min.	71	2.2
	max.	328	4.1
242	min.	104	2.2
	max.	287	6
147	min.	461	3.7
	max.	736	5.3
37	min.	644	6
	max.	819	12.9
42	min.	742	5.6
	max.	1429	7.6
Total	min.	34	2.2
	max.	1429	12.9

Predictive result

1. Initially, two measurements are taken, and it is then observed whether one of the following conditions is presented:

a. Both measurements have $CD4^+$ lymphocytes >500 cells/μL^3 and leukocytes >3.7 cells/mm^3.

b. Both measurements have a population of $CD4^+$ lymphocytes between 200 and 500 cells/μL^3 and at least one of the leukocyte measurements presents values ≥ 4 cells/mm^3.

c. Both measurements have a population of $CD4^+$ lymphocytes <200 cells/μL^3 and measurements of leukocytes between 2.0 and 3.9 cells/mm^3.

d. One of the measurements presents $CD4^+$ lymphocytes >500 cells/μL^3 and the other between 200 and 500 cells/μL^3.

e. One of the measurements presents $CD4^+$ lymphocytes between 200 and 500 cells/μL^3 and the other <200 cells/μL^3.

2. If condition *a* is presented, the greater probability is that in the posterior measurements, when leukocyte populations are ≥ 3.7 cells/mm^3, the associated $CD4^+$ populations will be >500 cells/μL^3.

3. If condition *b* is presented, the most likely event is that if in the following measurements leukocytes values are ≥ 4 cells/mm^3, the associated $CD4^+$ populations will be between 200 and 500 cells/μL^3.

4. If condition *c* is presented, the most likely event is that when a value of leukocytes between 2 and 3 cells/mm^3 in the following measurement is found, the associated $CD4^+$ populations will be <200 cells/μL^3.

5. If condition *d* is presented, and the values of leukocytes are between 3.0 and 3.9 cells/mm^3 and the following measurement is within that range, then the associated $CD4^+$ populations will be either >500 cells/μL^3 or between 200 and 500 cells/μL^3 but not <200 cells/μL^3.

6. If condition *d* is presented and the measurement that presents a value of $CD4^+$ between 200 and 500 cells/μL^3 also presents a value of leukocytes ≥ 4 cells/mm^3 and the measurement with a value of >500 cells/μL^3 also presents a value of leukocytes ≥ 3.7 cells/mm^3, then the most likely event is that $CD4^+$ values are between 200 and 500 or >500 cells/μL^3.

7. If condition *e* is presented and the value of leukocytes in the measurement that presents $CD4^+$ values <200 cells/μL^3 is <4 cells/mm^3, and if the measurement that presented a value of $CD4^+$ lymphocytes between 200 and 500 cells/μL^3 is linked to a leukocyte value ≥ 4 cells/mm^3 and in the following measurement a value of leukocytes is between 4 and 6 cells/mm^3 the most likely event is that the value of $CD4^+$ is found between [200, 500] cells/μL^3 but if the value of leukocytes is >6 a value of $CD4^+$ <200 cells/μL^3 can be found.

8. If condition *e* is presented, and the value of leukocytes in the measure that contains $CD4^+$ <200 cells/μL^3 is higher than 3 cells/mm^3, and for the registry of CD4+ between 200 and 500 cells/μL^3 a measure of leukocytes lesser than 3 cells/mm^3 is presented, it is more likely that if the value of leukocytes is higher than 3 cells/mm^3, then the measurement of CD4+ will be between 200 and 500 cells/μL^3.

As it was described above, two measurements of absolute leukocyte counts are first observed and then all the steps are checked in order to predict the CD4 + counts probabilistically in time. Thus, this procedure was applied to the remaining cases obtaining a predictive accuracy that varied between 0.96 and 1 for all the patterns for the ranges evaluated in time (Table 3).

Table 3
Values of probability for each of the ranges evaluated

Probability of accuracy of all patterns					
>500	[200,500]	<200	> 500 and [200,500]	[200,500] and < 200	Total
1	1	1	0.99	0.96	0.99

The sensitivity and specificity values obtained were 99%.

Discussion

This is the first investigation in which predictions for 5 types of dynamics of $CD4^+$ lymphocyte counts are conducted based on the absolute leukocyte count for the cases with counts > 500, between 200 to 500 and < 200 cells/μL^3 as well as for the counts that present fluctuations of values between 200 to 500 and > 500 and < 200 cells/μL^3 in 250 HIV-infected individuals in the context of probability theory, achieving a mathematical physical simplification of the phenomenon with a predictive precision of 99% with values of sensitivity and specificity of 99%.

With this methodology, mathematical relationships are established between the absolute leukocyte count and the CD4 + count along time in ranges of clinical interest. Since the values of probability were always above 0.96 and three of the types of dynamics have probabilities of 1, this suggest that the phenomenon itself presents a strong underlying deterministic order and that the method is highly accurate to predict the counts. Given these considerations, this methodology could be useful for clinicians to perform following ups of patients in time and to evaluate the effectivity of antiretroviral regimens, especially in low-income countries [13, 14], since only a complete blood count is required to establish measurements, which could also improve the medical assistance provided as well as patients' survival.

In other predictive research [7], the use of absolute leukocyte count has been proposed as a surrogate to establish the quantity of CD4 + cells, predicting counts < 200 cells/μL^3 with sensitivity and specificity values between 20.2% and 61%. Other predictive approximations have been conducted achieving more precise values [6, 15, 16] considering other markers such as the CD4+/CD8 + ratio [17] or the CD4 + percentage [18]. More recently, data mining algorithms such as Random Forest [19] have been developed to predict values of CD4 + < 100 cells/μL^3, obtaining a precision close to 100%. This algorithm implements rules that involucrate variables such as liver function, age, marital status, employment, education status, residence condition, functional status, WHO clinical stage, baseline and current antiretroviral regimen as well as time with treatment, baseline CD4/CD8 ratio, religion, weight, among others. In contrast, the developed methodology in this research offers a simplification of all these variables because it only requires a variable to predict CD4 + counts. Furthermore, this method distinguishes between ranges of clinical interest.

The mathematical thinking seeks to establish patterns, [20] this why when addressing a phenomenon as the one in this research, the efforts must be focused in establishing the right questions since they will allow to decide which is the relevant data from the one that is not, and in the case of medicine, this confers great utility. According to Frenkel: "my experience is that only about 10–15% of the information that the doctors collected was ever used when they made the diagnosis or treatment recommendations" [21] and "Yakov Isaevich used to say that doctors' thinking was well adapted to analyzing particular patients and making decisions on a case-by-case basis. But this also made it sometimes difficult for them to focus on the big picture and try to find general patterns and principles" which highlights the necessity of the mathematical thinking to find patterns that provide orders in the phenomena studied.

In this sense, the acausal impact of physics and mathematics is evidenced in the search of objective patterns that adequately describe distinct phenomena of nature. Following the line of thinking [12] different predictive methodologies have been developed that have addressed the problem of obtaining values of CD4 + lymphocyte counts from other variables. As an example of this, set theory has allowed to organize triplets of total leukocytes, lymphocytes and CD4 + counts to predict the counts of the last cellular line, with a precision up to 100% in specific ranges of leukocytes [22].

Conclusions

The implementation of the theory of probability allowed to establish a very precise and simplified approach to analyze the behavior of CD4 + lymphocytes and predict the value of this variable along time in HIV-infected individuals in ranges of clinical interest, relying only on the absolute leukocyte count. Thus, this method could be a useful tool in low-income settings where flow cytometry is not available, improving the surveillance and survival of patients.

Declarations

Ethics approval and consent to participate:

not applicable.

Consent for publication:

not applicable:

Availability of data and materials:

data will be made available upon request

Competing interests:

the authors declare that they have no competing interests

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Author's Contribution

JOR
Designed the study.

SEP
interpreted the mathematical results and developed the initial manuscript draft.

CEP
interpreted the clinical results and performed the statistical analyses.

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Figures

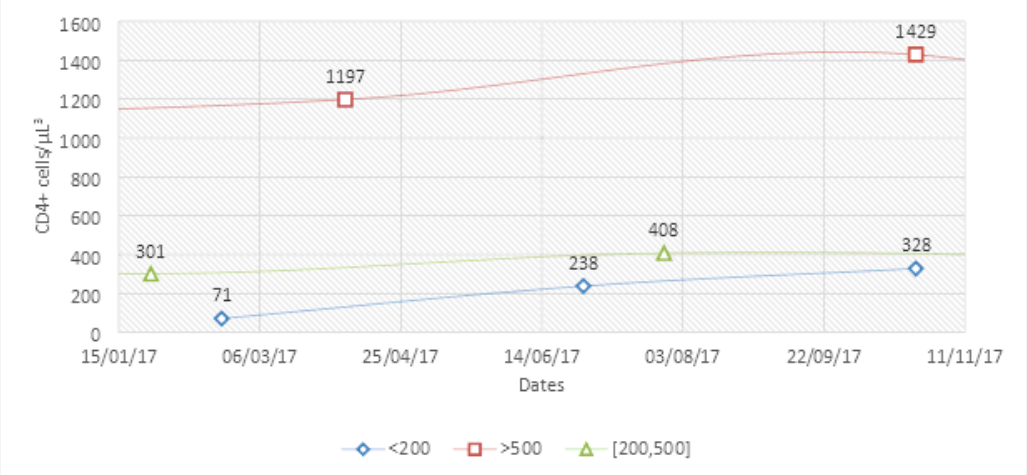

Figure 1

Dynamics for the cases that present values of CD4+ <200, between [200, 500] and >500 cells/µL3 for the cases 42, 135 and 245, respectively.

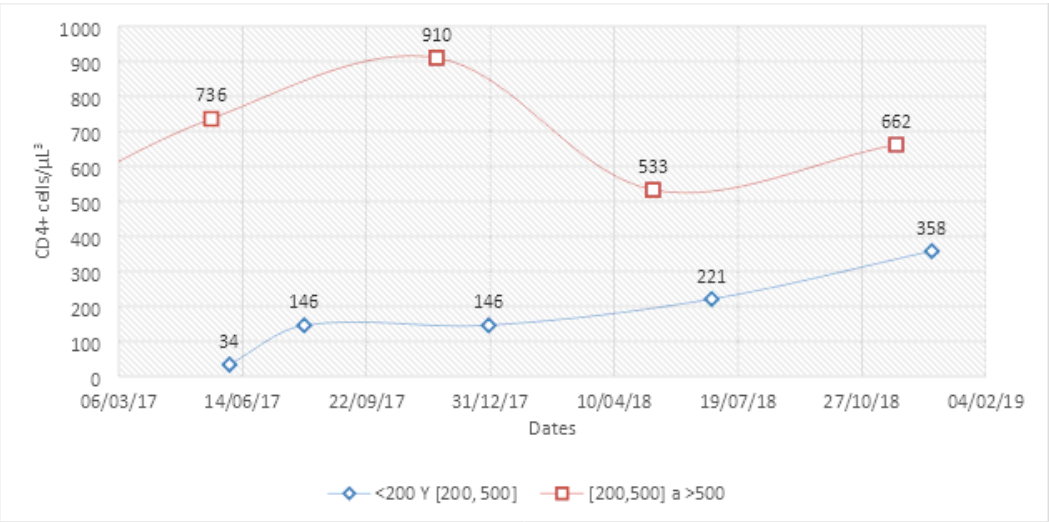

Figure 2

Dynamics for the cases that present values of leucocytes for the ranges <200, between [200, 500] and >500 cells/µL3 for the cases 42, 135 and 245, respectively.

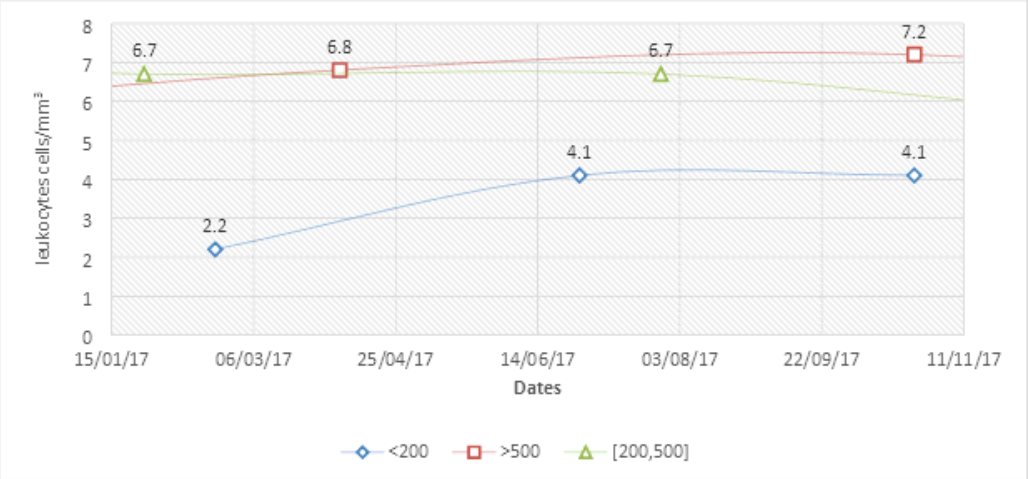

Figure 3

Dynamics of the values of CD4+ lymphocytes for the cases 147 and 234 that present fluctuations between [200, 500] to > 500 and [200, 500] to <200.

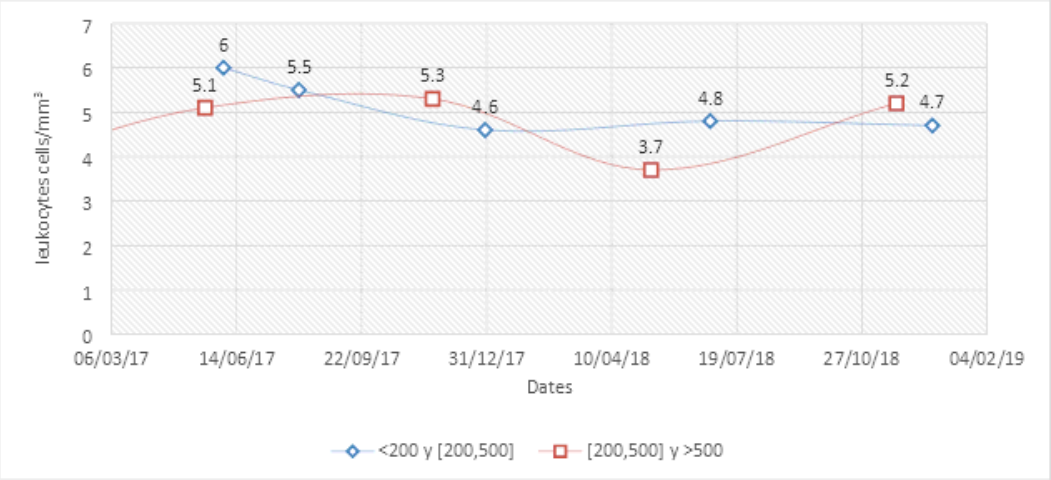

Figure 4

Dynamics of the values of leukocytes for the cases 147 and 234 that present fluctuations between [200, 500] to > 500 and [200, 500] to <200.