

# Predictive theory of CD4+ cells in HIV+ patients in antiretroviral therapy

Javier Rodríguez Velásquez (✉ [grupoinsight2025@gmail.com](mailto:grupoinsight2025@gmail.com))

Grupo de investigación insight <https://orcid.org/0000-0002-4585-3010>

Sandra Catalina Correa Herrera

Insight Group

Carlos Eduardo Pérez Díaz

Servicios y Asesorías en Infectología

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## Research article

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# Abstract

Background: Flow cytometry evaluates the number CD4-Positive T-Lymphocytes in patients infected with HIV/AIDS in anti-retroviral management, which orientates therapies towards different targets. Previously, a methodology was designed based on probability and set theories from leukocyte and lymphocyte counts of complete blood count, although predictions in time were not developed, which is why is wanted to establish a methodology of clinical applicability to temporarily forecast the values of CD4+ greater than 500, between 200 and 500 and lesser than 200 from the values of CD4+ and leukocytes of each patient. Methods: From sequential counts of CD4+ and leukocytes of 200 cases, the registries of 10 prototypical patients were observed to establish predictive patterns, and then these patterns were applied to the remaining patients in a blind study, finding the probability of success of the methodology as well as sensitivity and specificity values. Results: 5 patterns were found with percentages greater than 99% of predictive accuracy for the distinct conditions of the methodology, with values of sensitivity and specificity of 99%. Conclusions: through a mathematical theoretical simplification, a temporal self-organization in the sequence of measurements of leukocytes and CD4+ lymphocytes were established, highlighting the loading of probability in the dynamic of CD4+ counts, useful to conduct more appropriate following ups of patients in anti-retroviral management.

## Background

Nowadays, about 34 million people in the world live with HIV/AIDS, from which 7 of each 10 infected are between 15 and 49 years old according to recent reports of UNAIDS and United Nations (1). From 2001 it has been highlighted a decrease in the incidence of this disease in regions such as the Caribbean (42%) and Sub-Saharan Africa (25%). However, in other regions of the world the incidence since the 2000s, has been increasing, specifically in Middle East and North Africa as well as Eastern Europe and Central Asia. So, this pandemic continues to be a concerning issue for the sanitary and scientific community, generating a necessity of unifying efforts to increase the awareness of the risks, adequate prevention strategies and therapeutic assistance (2).

The recommendations of the World Health Organization (3) towards the remaining global institutions the deal with providing the initial anti-retroviral management as well as the following up of the patients are based in the absolute measurement of the number of CD4 lymphocytes, which is currently obtained through flow cytometry. Nevertheless, the technology that is required for this test is not only expensive in relation with the equipment required but because it requires highly qualified personnel. as a consequence, limited access is found in low income countries that do not possess the technological resources or the specialized personnel to perform the test (4).

Different strategies to overcome the difficulty off limited access to flow cytometry in low income countries have been developed. In the studies conducted with adults, it has been demonstrated that adequate correspondence can be established between the number of total lymphocytes and CD4<sup>+</sup> cells with values of sensitivity and specificity sufficiently acceptable to recommend it as a substitute of the

absolute count of CD4<sup>+</sup> lymphocytes (5–7). Likewise, studies in the pediatric population recommend using the count of total lymphocytes as a substitute for CD4<sup>+</sup> counts (8–9). On the other hand, different authors have focused in characterizing the variability of CD4<sup>+</sup> cell counts in both seropositive and seronegative patients with the purpose of developing predictive models of said variability and its relationship with life expectancy in HIV positive populations in Zambia and South Africa. However, the objective of this study what's not to establish a prediction of the value of CD4<sup>+</sup> cells but to predict possible effects of having one of these in seropositive population (10). Besides, it is important to consider that the life expectancy is of this disease and its variation can be characterized under different factors such as region, quality of life and the type of population studied. in a subsequent study, these authors developed a model to predict the count of CD4<sup>+</sup> cells from viral load With a performance of 87% (11).

Recent investigations have developed two types of predictive methodologies of the values of CD4<sup>+</sup> lymphocytes from set and probability theories. In the first scenario, set theory was established for the analysis of its properties, that is, the study of objects clearly defined based on notions such as belonging as well as axioms that establish mathematical relations between them, allowing the development of operations like union or intersection. From these promises, through the method of sets, the value of leukocytes and total lymphocytes were taken to predict the value of CD4<sup>+</sup> finding percentages of effectivity between 90% and 100% for leukocyte counts between 5000 and 4000 respectively (12). For the second case, with basis on probability theory, a prediction of the value of CD4 lymphocytes inferior to 570 CD4/ $\mu$ L from the counts of leukocytes and total lymphocytes inferior to 4000 with a probability equal to 1 (12). However, the predictions in intermediate ranges are not sufficiently high as to obtain clinical applications, which makes necessary a refinement of said methodology.

The purpose of this investigation is to develop a method to temporarily predict the population of CD4<sup>+</sup> lymphocytes in HIV-infected patients in antiretroviral management from the absolute leukocyte count of blood count.

## Methods

From a database evaluated by an specialist in infectious diseases of the enterprise “Servicios y Asesorías en Infectología”, 200 cases that had sequential registries were analyzed in time with different variables such as: absolute counts and percentages of TCD3<sup>+</sup>, TCD4<sup>+</sup> and TCD8<sup>+</sup> lymphocytes; CD4<sup>+</sup>/CD8<sup>+</sup> ratio and total lymphocytes; 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 ( $\log_{10}$ ); absolute counts of leukocytes, metamyelocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and reactive lymphocytes; erythrocyte sedimentation rate, mean platelet value and red blood count.

# Procedure

The acausal conception of theoretical physics through which this methodology is developed, implied a simplification of the conception of the phenomena, delimiting the observation of the behavior of the leukocyte count and CD4<sup>+</sup> cells. For this, an induction of 10 representative cases that capture the phenomena is developed in order to establish mathematical relations in form of patterns that are useful to predict CD4<sup>+</sup> cell counts from leukocyte counts, generating 5 possible dynamics:

1. Dynamics in which all the registries of the sequences present values of CD4<sup>+</sup> lymphocytes >500 cells/ $\mu$ L.
2. Dynamics in which all the registries of the sequences present values of CD4<sup>+</sup> lymphocytes between [200,500] cells/ $\mu$ L.
3. Dynamics in which all the registries of the sequences present values of CD4<sup>+</sup> lymphocytes lesser than 200 cells/ $\mu$ L.
4. Dynamics in which the registries of the sequences present values of CD4<sup>+</sup> lymphocytes >500 cells/ $\mu$ L3 but also between [200,500] cells/ $\mu$ L.
5. Dynamics in which the registries of the sequences present values of CD4<sup>+</sup> lymphocytes <200 cells/ $\mu$ L3 but also between [200,500] cells/ $\mu$ L.

Then, considering these groups, mathematical predictive patterns were found and a software in C<sup>++</sup> was developed that applied these parameters to conduct a blind study with the remaining cases of the study that were previously masked. Finally, the theory of probability is applied to calculate the possibility of success of the prediction for the totality of cases analyzed. It must be highlighted that the probability theory is the one that allows to develop a predictive methodology, as it does in quantum physics.

## Statistical analysis

The values of CD4<sup>+</sup> cells of the remaining cases not considered in the induction were unmasked in order to obtain true positives and negatives and false positive and negatives in a 2\*2 table, so sensitivity and specificity are calculated.

## Results

824 registries were analyzed corresponding to 200 patients, for which 73 cases had 1 registry, 45 cases had 2 registries, 52 cases had 3 registries, 65 cases had 4 registries, 37 cases had 5 registries and 10 cases had 6 registries. Some of the variables analyzed in different dates are exhibited with the case 117 (table 1).

After discriminating the variables of interest, the minimal and maximal values for CD4<sup>+</sup> counts were delimited, which oscillated between 34 and 1429 while the absolute values of CD4<sup>+</sup> lymphocytes oscillated between 2.2 to 12.9 (table 2). The evolution of these counts for some of the prototypical cases are observed in figures 1 and 2.

The values of accuracy of probability oscillated between 0.94 to 1 for the distinct cases with a general probability of 0.99 (see table 3).

## Predictive results

1. 2 measurements are taken, and it is looked whether one of the following configurations is presented:
  - a. Both have CD4<sup>+</sup> lymphocytes >500 cells/ $\mu$ L and leukocytes >3.7 cells/mm<sup>3</sup>.
  - b. Both have a population of CD4<sup>+</sup> lymphocytes between [200, 500] cells/ $\mu$ L and at least one of the leukocyte measurements presents values  $\geq$  4 cells/mm<sup>3</sup>.
  - c. Both have a population of CD4<sup>+</sup> lymphocytes <200 cells/ $\mu$ L and measurements of leukocytes between [2.0, 3.9] cells/mm<sup>3</sup>.
  - d. One of the measurements presents CD4<sup>+</sup> lymphocytes >500 cells/ $\mu$ L and the other between [200, 500] cells/ $\mu$ L.
  - e. One of the measurements presents CD4<sup>+</sup> lymphocytes between [200, 500] cells/ $\mu$ L and the other <200 cells/ $\mu$ L.
2. If case c is presented, the most likely event is that when a value of leukocytes between 2 and 3 cells/mm<sup>3</sup> in the following measurement, the associated CD4<sup>+</sup> populations will be <200 cells/ $\mu$ L.
3. If case a is presented, the greater probability is that in the posterior measurements, when leukocyte populations are  $\geq$  3,7 cells/mm<sup>3</sup>, the associated CD4<sup>+</sup> populations will be >500 cells/ $\mu$ L.
4. If case b is presented, the most likely event is that if in the following measurements leukocytes values are  $\geq$  4 cells/mm<sup>3</sup>, the associated CD4<sup>+</sup> populations will be [200, 500] cells/ $\mu$ L.
5. If case d is presented, and the values of leukocytes are between [3.0, 3.9] cells/mm<sup>3</sup> and the following measurement is within that range, then the associated CD4<sup>+</sup> populations will be >500 cells/ $\mu$ L or will be [200, 500] cells/ $\mu$ L.
6. If case d is presented and the measurement that presents a value of CD4<sup>+</sup> between [200, 500] cells/ $\mu$ L also present a value of leukocytes  $\geq$  4 cells/mm<sup>3</sup> and the measurement with a value of >500 cells/ $\mu$ L also presents a value of leukocytes  $\geq$  3.7 cells/mm<sup>3</sup>, then the most likely event is that CD4<sup>+</sup> values are between [200, 500] or >500 cells/ $\mu$ L.
7. If case e is presented, and the value of leukocytes in the measurement that presents CD4<sup>+</sup> values <200 cells/ $\mu$ L is <3 cells/mm<sup>3</sup>, and for the measurement that presented a value of CD4<sup>+</sup> lymphocytes between [200, 500] cells/ $\mu$ L has a leukocyte value  $\geq$  4 cells/mm<sup>3</sup>, if in the following measurement a value of leukocytes is between [4,6] cells/mm<sup>3</sup> the most likely event is that the value

of CD4<sup>+</sup> is found between [200, 500] cells/ $\mu$ L but if the value of leukocytes is  $>6$  a value of CD4<sup>+</sup>  $<200$  cells/ $\mu$ L can be found.

8. If case e is presented, and the value of leukocytes in the measure that contains CD4<sup>+</sup>  $<200$  cells/ $\mu$ L is higher than 3 cells/mm<sup>3</sup>, and for the registry of CD4<sup>+</sup> between [200,500] cells/ $\mu$ L a measure of leukocytes lesser than 3 cells/mm<sup>3</sup> is presented, it is more likely that if the value of leukocytes is higher than 3 cells/mm<sup>3</sup>, then the measurement of CD4<sup>+</sup> will be between [200,500] cells/ $\mu$ L.

## Discussion

This is the first investigation in which a predictive method of the number of CD4<sup>+</sup> cells is applied from probability theory, based on the number of leukocytes and lymphocytes of the complete blood count to evaluate temporal samples of patients. The reached predictions represent a solution against the problem of limited access to flow cytometry in low-income countries, allowing to achieve objective and trustable values in CD4<sup>+</sup> counts, developing the abstraction of different epidemiologic variables in a process of physical-mathematical simplification, achieving 5 dynamics. This might be useful to physicians, especially in low-income countries, in order to study the evolution of the disease in seropositive patients and consider early changes in antiretroviral regimens, which could improve the overall survival of patients, avoiding the appearance of opportunistic infections (13, 14).

The mathematical patterns found between leukocytes and CD4<sup>+</sup> cell counts as well as the high probability and accurate values for each of the ranges studied, since two were of 1 and the remaining above 0.94, suggesting that this phenomenon is highly deterministic. Different studies have been developed to substitute the value of CD4<sup>+</sup> cell through the absolute lymphocyte count (4–7, 15–17) as well as to predict the value of these cells through other variables as viral load (10), data mining (18) or CD4<sup>+</sup>/CD8<sup>+</sup> ratio (19). However, these proposals do not achieve adequate performances neither possess reproducibility among the different studies conducted, since they present variations according to age and populational groups studied. With this methodology, an abstraction of multiple variables that usually confuse and complicate the interpretation of phenomena is obtained.

However, it is highly useful to have methods that allow to predict the number of CD4<sup>+</sup> cells (20) at low cost and that are readily available for low-countries, particularly in high risk populations for an effective following up of the disease, such as the case of infected pregnant women (21) that can transmit disease to the fetus or, similarly, vulnerable communities of man that have sex with man, provided that people are willing to be treated. In this scenario, by only relying on the loading of probability evaluated in ranges, a simplification of multicausal considerations is performed, obtaining direct predictions. From set theory, predictions of the values of CD4<sup>+</sup> cells can be analyzed and established finding that values such as 570 cells can be predicted with a probability of 1 in ranges of leukocytes between 2999 or less (12). This acausal thinking of nature is the same that allowed the development of this investigation, with a main feature in common, that is the approaching a problem through the establishment of mathematical patterns and relations that can be generalized (22) and do not rely on epidemiological variables.

Different diagnostics and predictions of experimental and clinical applications have been developed in fields such as cardiology with a mathematical chaotic law and proportions of entropy (14, 15), differentiations of normal to neoplastic squamous cells of the cervix (25) and a generalization of the totality of fractal arteries in process of stenosis and restenosis (26). In public health, predictions of the outbreaks of malaria with accuracies up to 99.86% have been obtained (27), as well as in molecular biology (28) and mortality in ICU (29). These investigations corroborate that the acausal comprehension of phenomena in medicine from physics and mathematics, reveal underlying orders that can have practice applications.

## **Conclusions**

CD4+ cell count dynamics can be temporarily predicted through mathematical predictive patterns relying only on leukocytes counts of the complete blood count which would be highly beneficial in low-income countries where flow cytometry cannot be afforded in order to monitor patients in time and develop opportune strategies in order to opportunistically adjust antiretroviral therapy or initiate antibiotics. Besides, the high values of probability of these patterns strongly suggest that this phenomenon is deterministic.

## **Declarations**

## **Ethics approval and consent to participate**

This investigation is based on the ethical principles for investigation that involucre human beings of the World Medical Association's Declaration of Helsinki, the Nuremberg Code, and the Belmont Report. Following the scientific, technical and administrative regulations for investigation in health, stipulated in the Resolution 8430 of 1993 of Colombia, especially in the title 11, concerning to investigation with human beings, this investigation is classified un 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, respecting the integrity and anonymity of patients.

## **Consent for publication**

Not applicable.

## **Availability of data and materials**

The data that support the findings of this study are available from Servicios y Asesorías en Infectología but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Servicios y Asesorías en Infectología.

# Competing interests

The authors declare that they have no competing interests.

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# Authors' contributions

*JR* Designed the study, developed the methodology, analyzed the dataset and approved the final manuscript.

*SC* Designed the study, analyzed the dataset and prepared the manuscript.

*CP* Gathered data, analyzed the dataset, prepared, reviewed and approved the final manuscript.

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## Tables

**Table 1.** Sequential reports of the variables for the case p117.

Days elapsed		179	189	245	86	57	49
Date	1/11/2016	29/04/2017	4/11/2017	7/07/2018	1/10/2018	27/11/2018	15/01/2019
CD4+ lymphocyte count	196	254	372	199	169	225	172
Lymphocytes count	1.46	1.33	1.99	1.11	NA	1.48	1.01
Lymphocytes (%)	32.6	16.7	34.0	17.6	NA	41.5	25.3
CD3+ lymphocyte (%)	65.63	65.69	71.27	69.18	62.30	64.93	65.27
CD4+ lymphocyte (%)	12.57	16.09	20.42	17.21	14.10	15.58	17.13
CD8+ lymphocyte (%)	47.92	47.48	47.18	46.60	42.02	44.03	42.80
Reactive lymphocyte counts	0.04	0.03	0.03	0.04	NA	0.03	0.02
Reactive lymphocyte (%)	1.0	0.3	0.6	0.6	NA	0.7	0.5
CD3+ lymphocyte count	1027	1038	1299	799	748	938	657
CD8+ lymphocyte	750	750	860	538	505	636	431

<b>count</b>							
<b>Total lymphocyte count</b>	1565	1581	1867	1185	1201	1445	1007
<b>Lymphocytes count</b>	4.5	8.0	5.8	6.3	NA	3.6	4.0
<b>CD4<sup>+</sup>/CD8<sup>+</sup> ratio</b>	0.26	0.34	0.43	0.37	0.33	0.35	0.40

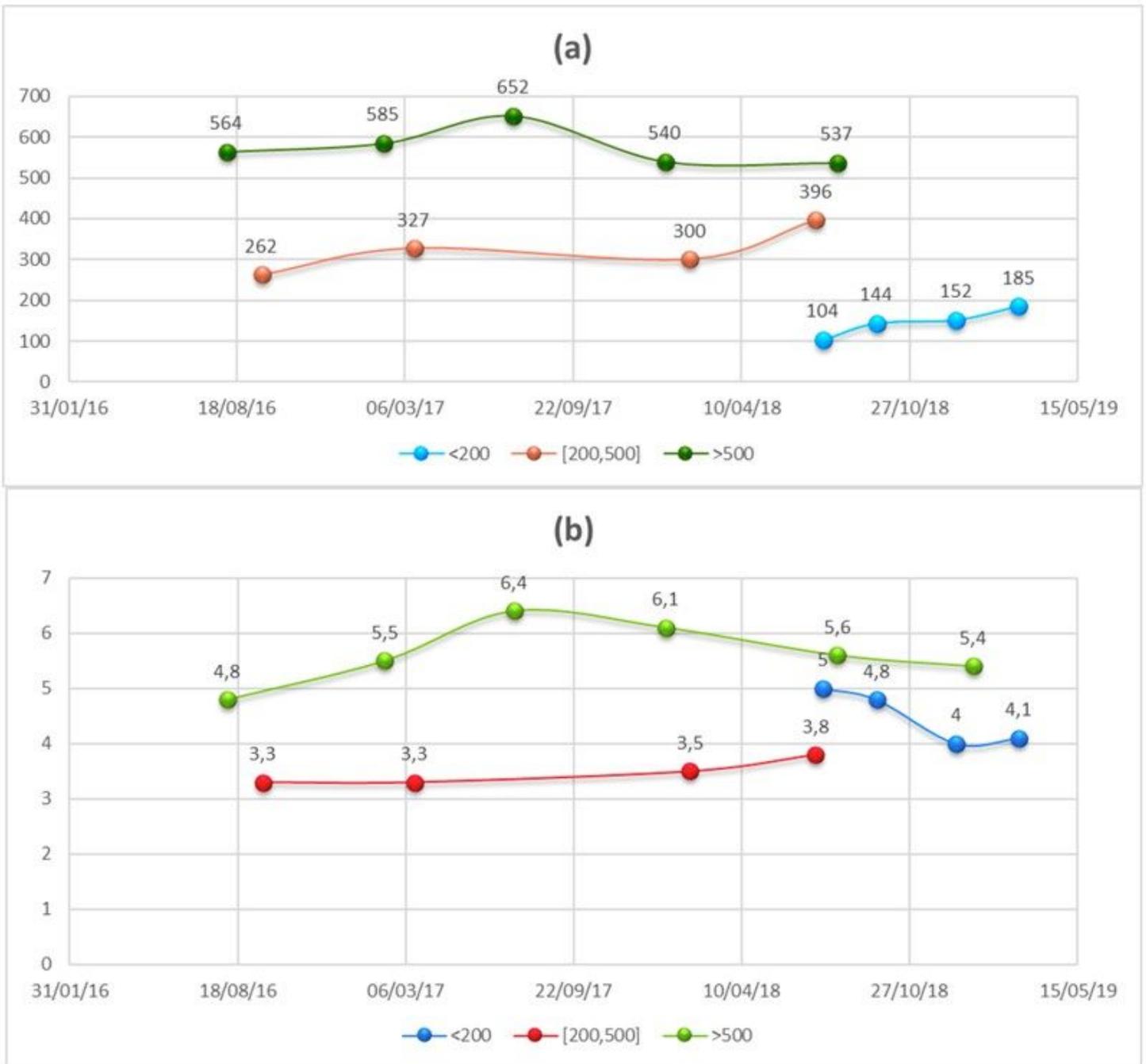
**Table 2.** Absolute CD4<sup>+</sup> and leukocyte counts for the prototypical cases of the sample analyzed.

Case		CD4 <sup>+</sup> (cells/ $\mu$ L)	Leukocytes (cells/mm <sup>3</sup> )
p5	min	644	6
	max	819	12.9
p25	min	742	5.6
	max	1429	7.6
p36	min	537	4.8
	max	652	6.4
p90	min	262	3.3
	max	396	3.8
p105	min	291	4.5
	max	491	8.8
p117	min	104	4
	max	185	5
p167	min	454	6.3
	max	582	8.3
p182	min	423	5
	max	660	8.1
p188	min	71	2.2
	max	328	4.1
p199	min	34	4.7
	max	358	6
Total	min	34	2.2
	max	1429	12.9

**Table 3.** Values of accuracy of probability for the predictions of the distinct established ranges.

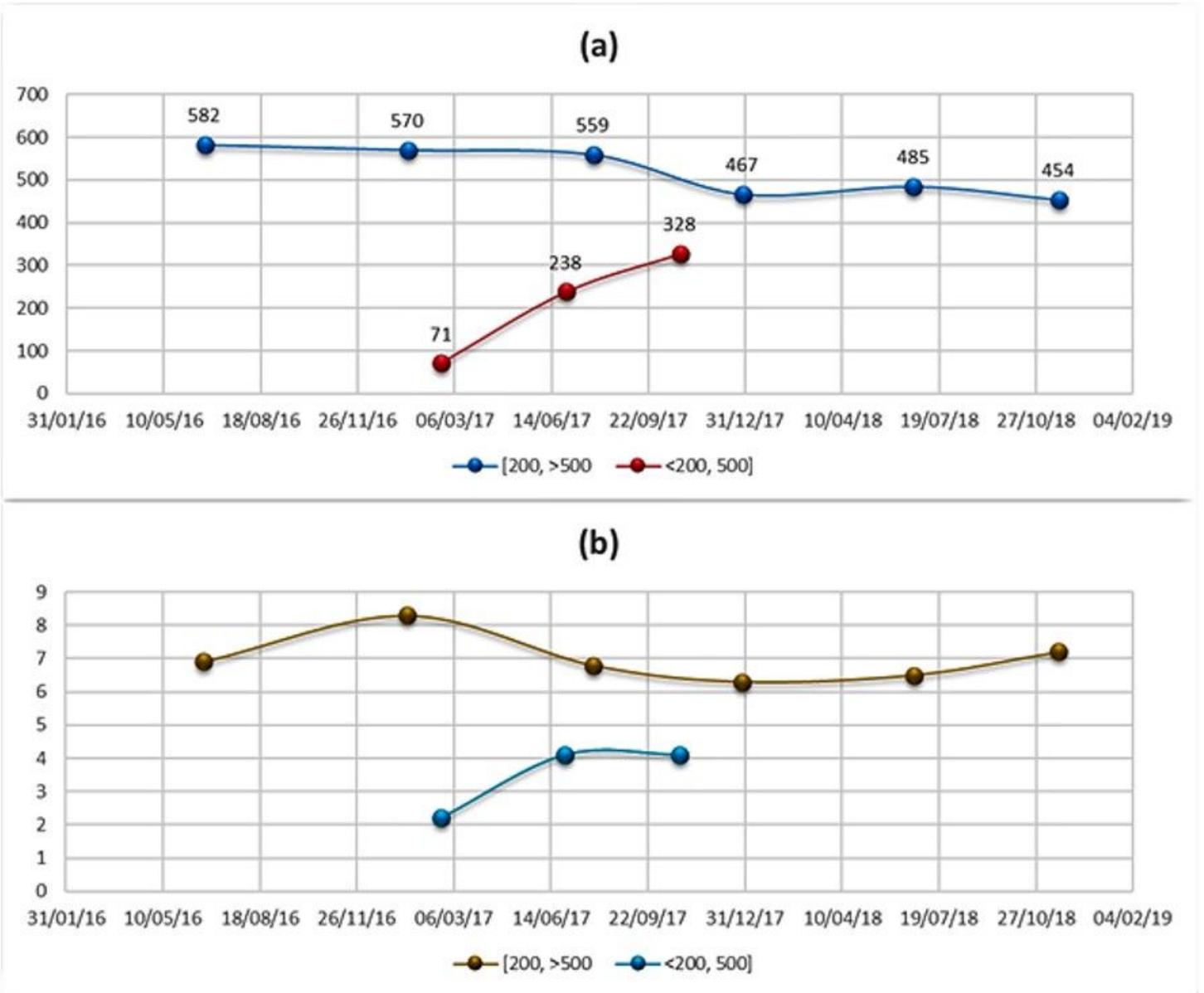
Values of probability for all the distinct patterns					
>500	[200,500]	<200	>500 and [200,500]	[200,500] and <200	TOTAL
1	0.97	1	0.98	0.94	0.99

# Figures



**Figure 1**

Representative dynamics of CD4+ lymphocytes (a) and leukocytes (b) of the cases p36, p90 and p117 with counts <200, between the range [200, 500] and >500



**Figure 2**

Dynamic fluctuations of CD4+ cell counts (a) and leukocytes (b) for the ranges between [200, 500] to > 500 of the case p167 and [200, 500] to <200 of the case p188 (b).