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Full Length Research Paper

Modeling of nevirapine-based antiretroviral regimen response by taxonomy from different CD4 cell counts strata

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The search for determinants responsible for changes in CD4 cells count can help to optimize the efficiency of the nevirapine-based antiretroviral therapy in Côte d'Ivoire. Our study on the response to this treatment was carried out through taxonomy of CD4 cells count trajectories using non-hierarchical-descendant model. One hundred and sixty four patients were grouped according to their baseline CD4 count in three strata (<100/mm^3, 100-200/mm^3 and >200/mm^3). In each category, classes of similar CD4 count trajectories represented by standard paths called meta-trajectories have been formed by the model and we have searched for the determining factors. On the overall, there was a significant variation between classes (p<0.001) of the following variables: average CD4 count, nadir CD4, peak CD4, average CD4 gain. According to the profile of meta-trajectories, CD4 cells gains are obvious during the first six months of treatment, and then changes are variable according to classes regardless of the baseline CD4 count. The other medical follow -up variables showed no significant variation between classes in the categories of initial CD4 count 100/mm^3. However in patients with baseline CD4<100/mm^3, variables like mean weight (p=0.04), mean hemoglobin count (p=0.01) and average gain of hemoglobin (p=0.03) are also explanatory of partition into different classes. Baseline characteristics showed no significant variation between the different classes in the categories of initial CD4 count 100/mm^3. However for patients with baseline CD4 count<100/mm^3, sex is explanatory of classes partition (p<0.05) . Correspondence analysis revealed other determining factors related to the different meta-trajectories (initial CD4 count, initial CD4 cells percentage, adherence, presence, or absence of opportunistic infections prior to the treatment). These factors influencing the CD4 cells response of nevirapine-based regimen in Côte d'Ivoire must be considered to maximize efficiency of the treatment.

Key words: Nevirapine, CD4 cells count response, meta-trajectories, Non-Hierarchical-Descendant Model, antiretroviral regimen.

INTRODUCTION

Sub-Saharan Africa remains the global epicenter of the pandemic of HIV/AIDS. Côte d'Ivoire is one of the countries most affected by the HIV/AIDS. In 2007, the UNAIDS reported a prevalence of HIV in the general population estimated at 3.9% (ONUSIDA, 2007). AIDS is a major public health problem in this country. In HIV/AIDS, the extent of plasma viral load and CD4 cell count are the main parameters used in monitoring patients and their treatment. Today, the initiation or modification of antiretroviral therapy is guided by value and/or the changes in these markers. The changes in these markers, especially antiretroviral therapy, are the focus of interest of many studies whose main objective is to understand the determinants (Thiébaut, 2002). Indeed,

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the dynamics of clinical and biological criteria can vary independently of the intrinsic efficacy of antiretroviral therapy, due to the influence of other parameters specific to the patient or related to the therapeutic environment. In Côte d'Ivoire, modeling studies in bio-clinical and therapeutic monitoring of patients are rare. In clinical research, modeling stage is fundamental because it can summarize mathematically the situation and tries to give a rigorous solution which can ensure the efficiency of antiretroviral treatment. The search for determinants of deleterious changes in medical markers might enhance optimizing treatment efficiency. The taxonomy which signifies etymologically "science of the laws of classification" is made up of different methods of automatic classification (Paturel, 1979; Petit et Dussart, 2005). The changes in quantitative medical data with time may be represented by curves or paths. By grouping similar trajectories in homogeneous bundles, it is possible to highlight standard paths or meta-trajectories. Each meta-trajectory corresponds to different classes of patients with a similar pattern of medical data. It seems so interesting to assign to these classes, specific characteristic or explanatory factors. The identification of favorable or unfavorable factors of the evolution of certain quantitative medical parameters can help in the monitoring of these patients by prediction before the start of treatment or by deduction during treatment. The modeling process related to the Non-Hierarchical-Descendant (NHD) algorithm is an appropriate method of taxonomy to seek for independent trajectories group related to different groups of patients (Petit and Dussart, 2005). This model addressed the problem of classification of PLWAs (people living with HIV/AIDS) according to the evolution of immunological markers during antiretroviral therapy**.** Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are a key class of effective antiretroviral drugs (ARVs) used in the composition of first- line regimens combined with two Nucleoside Reverse Transcriptase Inhibitors (NRTIs). They can easily be incorporated in not too complex initial antiretroviral regimens. Nevirapine (NVP), since its first description as NNRTI (Merluzzi et al., 1990) has proven its effectiveness when used in appropriate combined regimens. A large randomized test has compared nevirapine and efavirenz (EFV) in a tritherapy combined with stavudine (d4T) and lamivudine (3TC) (Eth et al., 2004). This test showed that the rate of virologic failure was not significantly different between patients receiving nevirapine and those receiving efavirenz. These equally effective NNRTIs, may be substituted for each other in case of poor tolerance, for example in case of persistent and severe toxicity of efavirenz on the central nervous system, although it was noted in women with more than 200 CD4/mm^3 (the most significant rash while using nevirapine than efavirenz) (Eth et al., 2005). NVP remains the NNRTI of choice for women in case of potential pregnancy or during their first trimester of pregnancy, EFV should be rejected because of its teratogenic effect (OMS, 2008). Nevirapine is widely available and has a lower cost than EFV. In addition, important experience has been gathered on its use in developing countries. However, the efficiency of nevirapine-based antiretroviral regimen in these countries necessarily requires the search for determinants of treatment optimization. This minimizes any cross-drug resistance in the group of NNRTIs. In Côte d'Ivoire, ordinary HIV1-infected adult patient (not pregnant for example) can take as a first line treatment, one of the two alternatives of 2NRTIs +1NNRTI association that is, 2NRTI + EFV or 2NRTI + NVP. We are interested in studying the therapeutic response of the association 2NRTI + NVP from the taxonomy of CD4 cells count trajectories with NHD classification model in order to investigate the determinants in naive symptomatic patients in Abidjan (Cote d'Ivoire).

MATERIALS AND METHODS

Type of study

It is a modeling study of CD4 cells count trajectories to evaluate the response of nevirapine-based antiretroviral regimen using a Non-Hierarchical-Descendant process (NHD).

Patients and biomedical data

The biomedical data underlying this modeling are from a longitudinal observational database of bio-clinical and therapeutic monitoring of outpatients on antiretroviral therapy for at least two years. This observational study was conducted in clinical centers accredited in the care of patients living with HIV/AIDS in Abidjan: Ambulatory Care Unit and Advice (USAC) and the Integrated Centre for Bioclinical Research of Abidjan (CIRBA). This clinical study was carried on patients infected with the Human Immunodeficiency Virus type 1 (HIV-1). The study involved outpatients aged at least 15 years (adolescents and adults) of both sexes whose therapeutic care began in 2006 to 2007. We considered patients naïve to antiretroviral treatment at M0 (prior to initiation of treatment). Pregnant women were excluded from the study. In accordance with the eligibility criteria for adolescents and adults in Côte d'Ivoire (Eholié and Girard, 2005), we considered symptomatic patients (CDC Stage B) with baseline CD4 count of <350/mm^3. This category of patients was the highest among eligible PLWAs for antiretroviral treatment in our study. The regularity in medical monitoring as regards to medical visit dates was the first criterion for selection after analysis of medical records. The next medical visits were an opportunity to give them questionnaires if they are willing: a refusal was a factor for exclusion from the study. Patients with irregular medical visits or loss of contact have been excluded from the study because follow-up should be scheduled for two years to avoid missing biomedical data during this period. Patients were alive throughout the monitoring period. Adherence was assessed every three months. Concerning the medical doctors, adherence has been assessed based on the following criteria:

Regularity in clinical follow-up appointment; questioning the patient about the doctor's recommendations on dosages, conditions and time for taking the prescribed drug; counting of drugs but not systematically for all the patients; a patient is declared to be good compliant if he/she has taken a value of >90% of his/her total tablets. When in doubt due to a static CD4 level or decreasing with

high viral load and the doctor called the pharmacy to inquire about the date of the last visit of the patient. In this case the patient is considered as non-compliant if not regularly going to the drugstore for the renewal of his/her drugs.

The status of anemic prior to treatment was defined using the following criteria:

Adult males; hemoglobin rate <13 g/dl, adult non-pregnant women; hemoglobin rate <12 g/dl (WHO/UNICEF/UNO, 1998). The initial clinical condition is said to be good if (no asthenia, weight loss and prostration), average (moderate signs of the triad; asthenia, weight loss and prostration) or bad (severe signs of the triad; asthenia, weight loss and prostration).

The counting of CD4 cells was done by the technique of flow cytometry. A database was constituted with socio-demographic, biomedical and therapeutic information after the observational clinical study.

In this observational database, we selected for this study, 164 symptomatic patients (Stage CDC B) with nevirapine-based antiretroviral regimen.

The biomedical data used for the treatment of those results relate to M6 (sixth month), M12 (twelfth month), M18 (the eighteenth month) and M24 (twenty-fourth month) after initiation of treatment and those of M0. The taxonomy of CD4 cells count trajectories by NHD model was applied to all patients in each initial CD4 count stratum (<100/mm^3, 100 to 200/mm^3 and >200/mm^3).

NHD method, trajectories and meta-trajectories of CD4 cells counts

We defined I = {1,…, i, …, n} as the set of all trajectories to be classified and E = {a_1 , a_2,…,a_n} sets of values of criteria of efficiency, with a_i = (a_{i1}, a_{i2},…,a_{ip}); all values of efficiency criteria for a given patient i: in our case one criterion was considered (CD4 cells count). It is necessary that at each point a_{ij} match the same abscissa regardless of the patient i: test of effectiveness must be evaluated at a common frequency for all patients. We have considered a six-monthly periodicity.

The main measure of antiretroviral response, the CD4 count, is determined every six months, like most other biological monitoring criteria. Clinical follow-up is usually done every three months but we considered the semester clinical criteria values in order to harmonize the frequency of criteria. A bundle represents a class of trajectories grouped by the algorithm. Each class is represented by its center of gravity. This provides a graphical trend of the temporal evolution of CD4 count (meta-trajectory) of a group of patients. To each given meta-trajectory of CD4 count, is assigned a set of characteristics related to a group of patients in the form of quantitative or qualitative variables. Apart from CD4 counts whose values at M0, M6, M12, M18, M24 were used to determine individual trajectories, other variables related to baseline characteristics and treatment monitoring have not been used for classification and have only served to give a better description of the classes. The explanatory variables can be determined from all the characteristics assigned to each group of a given meta-trajectory of CD4 count. These variables are statistically related to the partition. The NHD process has been devised and developed by Fages (Paturel, 1979).

The basic theory of algorithm from this model of taxonomy, takes into account the following main parameters.

Considering P (a partition with size q), A (a class of size n), m_i (the weight of an element) m_A (the weight of a class which represents the sum of the weights of its elements): is called a partition P on set E; P = {A_i} with i = 1…q as:

$$\forall i = 1 \dots q \qquad A_i \neq \emptyset$$
$$\bigcup_{i=1}^{q} A_i = E$$
$$A_i \cap A_j = \emptyset \qquad \forall i \neq j$$

The number q is not known and it must be determined.

We define the center of gravity of the class A by:

$$g(A) = \frac{(\sum_{i=1}^{n} m_i x_i)}{m_A}$$

Inertia (average of the square of distances from points of class A to center of gravity of the cloud) is given by:

$$I(A) = \sum_{i=1}^{n} m_i d^2(x_i, g(A))$$

Inertia is a real number. It measures the dispersion of a cloud of points. We used the inertia as the dispersion with the algorithm of NHD classification. The option of Euclidean distance was chosen in the classification algorithm NHD:

$$d(a, b) = \sqrt{\sum_{i=1}^{n} (a_i - b_i)^2}$$

The sum of inertia of each class is the within-class inertia: $I_W = \sum_{i=1}^{q} I(A_i)$ (Within).

If the cloud of points is composed of k classes note A_1 , A_2, …, A_k, they will be more homogeneous if the inertia of each class I(A_1), I(A_2), …, I(A_k) respectively calculated relative to their respective centers of gravity g(A_1), g(A_2), …, g(A_k), are low. The dispersion of classes from the center of gravity of the cloud is called the inter-class inertia and is defined by:

$$I_B = \sum_{i=1}^{q} m_{A_i} d^2(g(A_i), g(E))$$ (between)

The explanatory power or partition score (P_E) is defined as the ratio between the inter-class inertia and the total inertia thus: $P_E = I_B / I(E) = I_B / I_W + I_B$ because $I(E) = I_B + I_W$.]

The quality of the partition is determined by the value of the explanatory power or score of partition from 0 to 1. The score of partition with a value close to 1 implies a good separation of groups. On the contrary, values close to 0 implies a lower homogeneity. The classical approach to NHD classification requires the use of more tests with different numbers of classes. In solution to this problem, the decrease in inter-class inertia allows stopping the classification process: when the decrease is no more significant, the number of classes obtained is satisfactory. The incremental aspect of the algorithm is very convenient because it allows finding the successive partitions for different numbers of classes. The algorithm provides after each increment, an optimal partition (from the partition in 2 classes to q_{max} classes). The algorithm stops when:

$$\frac{I_B(P_n) - I_B(P_{n+1})}{I_B(P_n)} < d$$

where d is a threshold set by the user and I_B Inter-class inertia of the partition.

We call this method, NHD incremental method. The results are

Table 1. Patients baseline features.

Patients baseline features	n(%) or median (IQR)
Female	114 (69.5)
Good general condition	57 (34.8)
Presence of OI prior to antiretroviral therapy	84 (51.2)
AZT+3TC+NVP	3 (1.8)
D4T+3TC+NVP	161 (98.2)
Prophylaxis with cotrimoxazole	153 (93.3)
Age (years) at treatment initiation [Median (IQR)]	39 (33-44)
Weight, kg [Médian (IQR)]	56 (48.2-63)
Baseline Karnofsky score [Median (IQR)]	90 (90-100)
Baseline CD4 cells count /mm^3 [Median (IQR)]	156 (84.5-230.5)
Baseline CD4 cells count < 100/mm^3	50 (30.48)
Baseline CD4 cells count [100-200/mm^3]	53 (32.32)
Baseline CD4 cells count > 200/mm^3	61 (37.20)
Baseline CD4 cells percentage [Median (IQR)]	8 (5-13)
Baseline Hb count (g/dl) base [Median (IQR)]	10.6 (9.4-11.6)
Baseline MCV (fl) [Median (IQR)]	83 (77.3-87.4)

OI, Opportunistic infections; IQR, interquartile range; Hb, hemoglobin.

satisfactory for a threshold of 0.1 (Petit and Dussart, 2005). We shall later use the NHD algorithm with the following parameters: incremental method, inertia as dispersion, Euclidean distance, setting off at 0.1, rejection at 0.3 and 1 as a minimum size per class.

Variables selected for the characterization of classes by taxonomy

In the context of developing countries like Côte d'Ivoire, the determination of CD4 count is recommended in the therapeutic monitoring of PLWAs. CD4 cells count trajectories were used for classification, but other variables affiliated to this parameter were used to characterize different classes: median CD4 cells count, CD4 cells gain (between M0 and M24), Nadir CD4 count, CD4 count peak during treatment for the values considered at M6, M12, M18 and M24. We have also considered other follow-up parameters: CD4 cells percentage, mean weight, weight gain (between M0 and M24), Karnofsky score, hemoglobin count, hemoglobin gain (between M0 and M24), mean corpuscular volume (MCV) and MCV gain (between M0 and M24). Other variables such as "substitution of ARVs" and adherence were considered. The baseline characteristics were considered for correlation analysis with CD4 cells count meta-trajectories: age, sex, weight, general condition, Karnofsky score, CD4 percentage, initial CD4 count, hemoglobin count, MCV rate, presence of opportunistic infections (OI) before highly active antiretroviral therapy.

Statistical analyses

The median values were considered for quantitative variables, the percentages and numbers for qualitative variables. The SPSS Software Version 14.0 was used for statistical analyses (descriptive statistics, chi -square test, Fisher test and Kruskal-Wallis test). The threshold for significance was 5% in all tests. The MCA (Multiple Correspondence Factor Analysis) was used for further analysis to clarify the correlations between variables and classes of patients according to their CD4 cells count meta-trajectory. The SPAD 4 Software was used for MCA.

RESULTS

Baseline demographic, clinical and therapeutic features

A total of 164 patients were selected for this study. The distribution of patients according to their initial CD4 count (<100/mm^3, 100 to 200/mm^3 or >200/mm^3) was more or less homogeneous. Their antiretroviral therapy was NVP associated with 2NRTIs: AZT + 3TC (1.8%) or D4T + 3TC (98.2%). The average age was 39 years old and 69.5% were female. All the baseline features of the patients are presented in Table 1.

NHD process

Analysis of different CD4 cells counts meta-trajectories

Tree, in each group of patients that takes into account various levels of classification with an increasing number of classes from one partition to another is shown in Figure 1.

***In the category of patients with initial CD4 count <100/mm^3*:** Five classes have been determined with a score of partition equal to 0.71. All CD4 cells count trajectories are presented and five meta-trajectories were

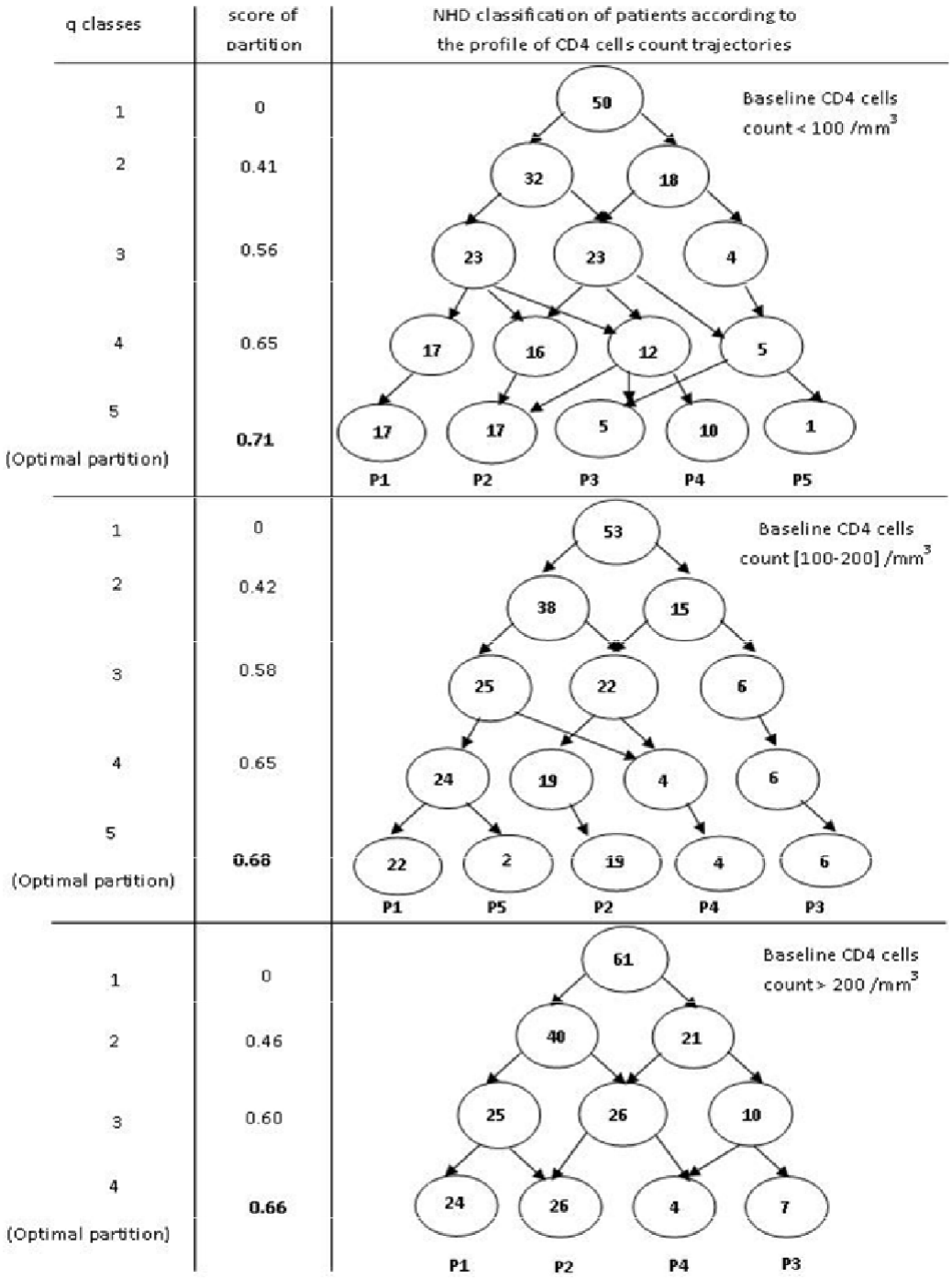

Figure 1. Trees observed from NHD process applied to CD4 cells count trajectories with different baseline CD4 cells count categories.

determined by the model (Figure 2). To each of these meta-trajectories corresponds a class of patients with the following number of patients: P1 (n = 17), P2 (n = 17), P3 (n = 5), P4 (n = 10), P5 (n = 1). The class P5 resulted in one patient whose CD4 count trajectory is unique and quite distinct from the others. The meta-trajectory that seems most interesting is that of Class P3.

***In the category of patients with initial CD4 count between 100 and 200/mm^3*:** Five classes have been determined with a score of partition equal to 0.68. The

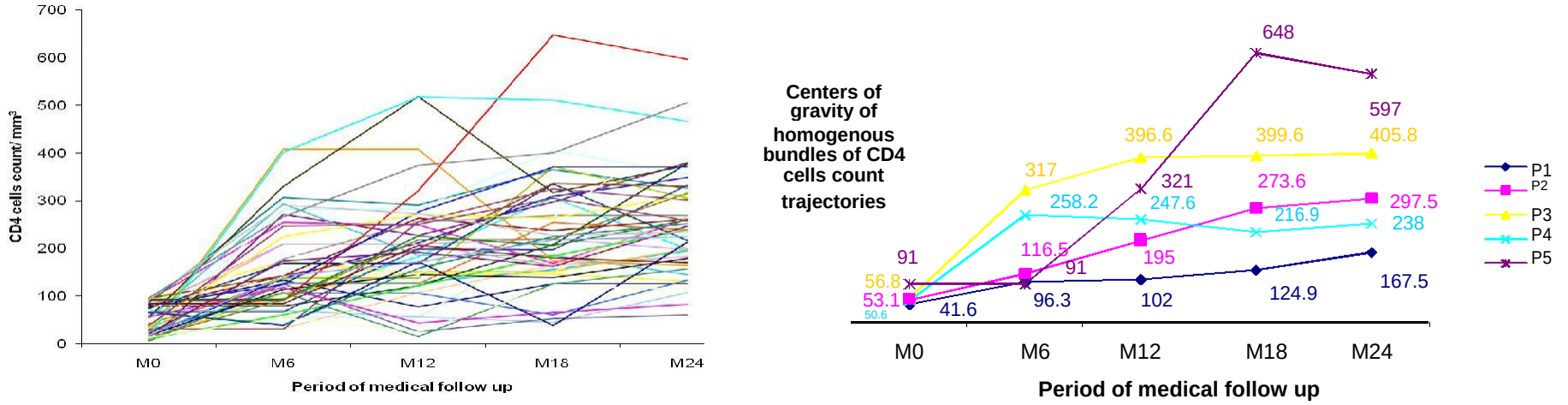

Figure 2. Trajectories and meta-trajectories of CD4 cells count of patients with baseline CD4 cells count <100/mm^3.

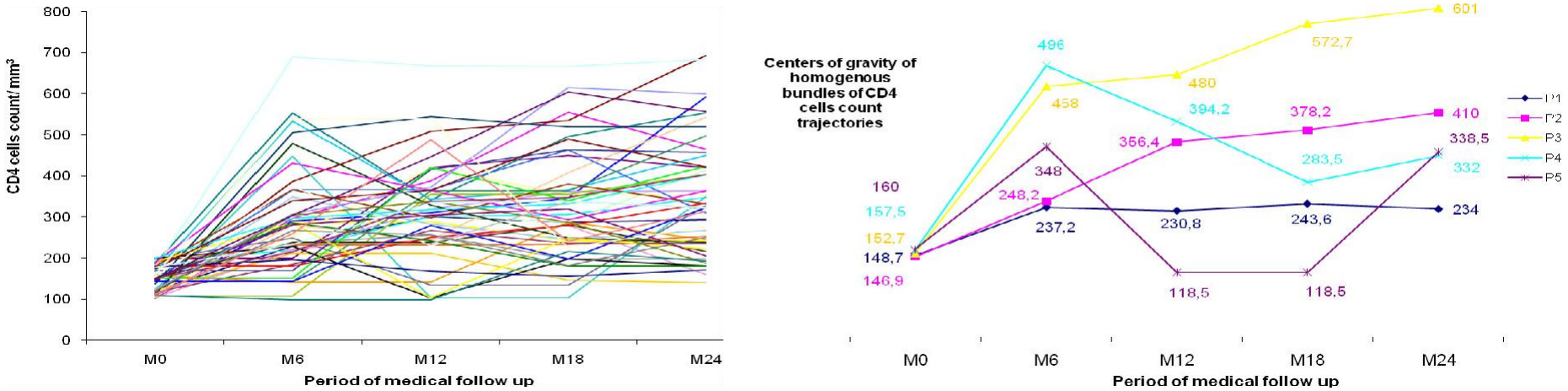

Figure 3. Trajectories and meta-trajectories of CD4 cells count of patients with baseline CD4 cells count between 100 and 200/mm^3.

whole CD4 cells count trajectories are shown in Figure 3 and five meta-trajectories were determined by the model (Figure 3). Five meta-trajectories were determined (Figure 3) by the model. To each of these meta-trajectories corresponds a class of patients with the following numbers: P1 (n = 22), P2 (n = 19), P3 (n = 6), P4 (n = 4), P5 (n = 2). The meta-trajectory that seems most interesting is that of Class P3.

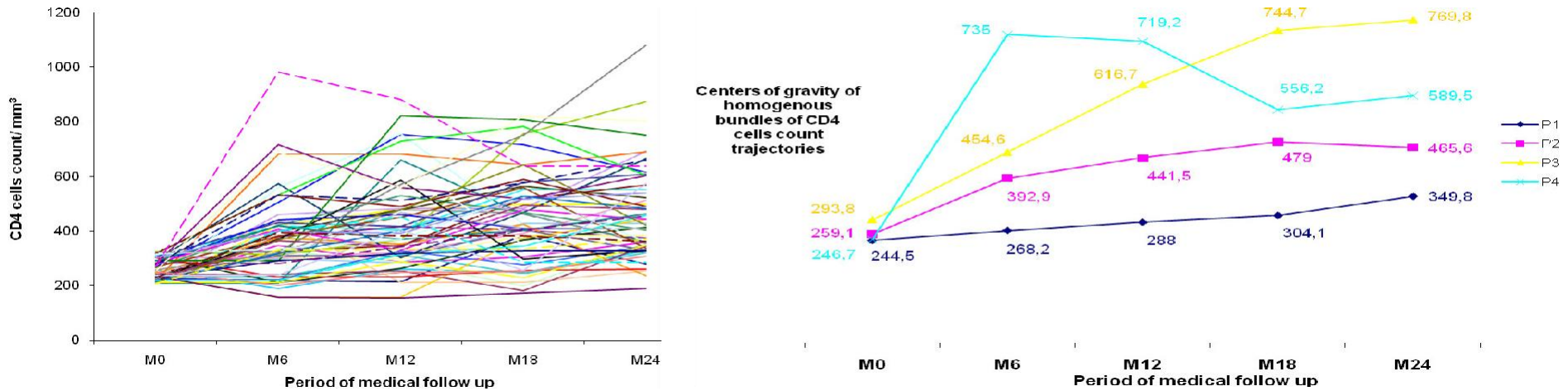

Figure 4. Trajectories and meta-trajectories of CD4 cells count of patients with baseline CD4 cells count >200/mm^3.

In the category of patients with initial CD4 count>200/mm^3: Four classes have been determined with a score of partition equal to 0.66. All CD4 cells count trajectories are presented and four meta-trajectories were determined by the model (Figure 4). To each of these meta-trajectories corresponds a class of patients with the following numbers: P1 (n = 24), P2 (n = 26), P3 (n = 7), P4 (n = 4). The meta-trajectory that seems most interesting is that of Class P3.

Analysis of medical follow-up characteristics of patients according to baseline CD4 cells stratum

The complete statistical description of medical follow-up variables is shown in Table 2. In each category of initial CD4 count, there is significant variation between classes (p<0.001), for all variables affiliated to the main treatment response criterion used in the partition: that is median CD4 count, Nadir CD4 count; the peak of CD4 and CD4 gain values. The classification into distinct meta-trajectories thus appears as the result of a physical reality, not an arbitrary division into classes from the trajectories of CD4 counts. Other variables of treatment follow- up that have not been used in partitioning, but considered in the description of the groups showed no significant variation between different classes in the categories of initial CD4 count 100/mm^3 (100 to 200/mm^3 and >200/mm^3). In these categories, the various classes of patients are homogeneous according to these other patients monitoring parameters. The initiation of antiretroviral therapy has certainly helped to improve these parameters in each group, to make them homogeneous. Apart from variables related to CD4 count, no other variable of treatment follow-up is explanatory of partition into different classes from the model. However, in the category of patients with initial CD4 count <100/mm^3, other variables of treatment follow-up are explanatory of partition of patients into five classes with a significant variation between these classes. These variables are: average weight (p = 0.04), average hemoglobin count (p = 0.01) and average hemoglobin gain (p = 0.03).

Analysis of baseline characteristics of patients according to their baseline CD4 category

The complete statistical description of the baseline features is shown in Table 3. These variables that were not used in partitioning, contributed to a better description of the classes in order to highlight those that were also explanatory of the different partitions. These basic features showed no significant variation between the different classes in the categories of initial CD4 count 100/mm^3. In these categories, the various classes of patients differ slightly depending on the basic features considered. On the other hand, in the category of patients whose initial CD4 count is

Table 2. Medical follow up characteristics by NHD classes according to baseline CD4 cells count category.

Baseline CD4 cells count category	Classes from NHD model	Median (IQR)										
		Mean CD4 cells count	CD4 Nadir	CD4 Peak	Mean CD4 gain	Mean weight	Mean weight gain	Mean SK	Mean Hb count	Mean Hb gain	Mean MCV	Mean MCV gain
< 100 /mm^3	P1a (n=17)	137.5	60	179	129	56.2	1	97.5	12.3	2	97.8	19.2
(a) (N=50)		(89.8-151.5)	(35-110)	(129-217)	(52.5-187)	(50-59.2)	(-3.5-7.5)	(95-100)	(11.2-12.9)	(1-2.8)	(89.1-104.5)	(12.8-21.1)
	P2a (n=17)	222.5 (195.7-247)	126 (85.5-142.5)	325 (261.5-359)	266 (191-294)	62.5 (54-71.2)	2 (0-11)	97.5 (95-100)	12.2 (11.1-13.5)	2.65 (1.6-3.6)	96.9 (88.3-105.6)	17.8 (14.1-20)
	P3a (n=5)	385 (326.6-442.7)	291 (274-359)	506 (385-518)	329 (278.5-433)	71.5 (59.6-80.7)	9 (5-20)	100 (98.7-100)	13.4 (11.8-14.3)	4 (3.1-5.1)	93.4 (86.6-99)	16,8 (8.9-20.2)
	P4a (n=10)	244.8 (200.1-273.2)	182.9 (164.2-227)	292 (239.7-328.7)	155 (120.2-237.5)	66.4 (61.2-73.5)	8 (1.7-11.7)	100 (98.7-100)	14.2 (13.3-15.1)	3.2 (2.1-4.1)	101.7 (95.4-103.6)	15.2 (11.8-21.1)
	P5a (n=1)	414.2	91	648	506	57.5	-4	97.5	11.5	4.8	90.3	13.1
	p	**< 0.001**	**< 0,001**	**< 0.001**	**< 0.001**	**0.04**	0.05	0.22	**0.01**	**0.03**	0.60	0.82
100-200/mm^3	P1b (n=22)	236.7	183.5	286	85.5	62.2	5.5	97.5	12.4	2.3	94.6	13.2
(b) (N=53)		(212.5-278)	(143.5-230.5)	(255.2-325.7)	(36-142.1)	(59.6-67.1)	(1.7-8)	(95-100)	(11.4-13.2)	(1.3-3.1)	(86.6-101.8)	(9.9-19.2)
	P2b (n=19)	341.7 (325.5-377)	244 (200-297)	424.2 (380-490)	250 (201-302)	56.7 (49.7-65.2)	4 (3-10)	97.5 (95-100)	12.6 (11.4-13.8)	3.4 (1.8-3.7)	94.8 (85.7-99.2)	15.3 (8-18.3)
	P3b (n=6)	504.4 (476.7-566.9)	363.5 (307-546)	609.5 (551.5-690.5)	442 (378.2-518.7)	59.7 (54-70.1)	-2 (-4.2-5)	97.5 (93.7-100)	12.7 (11.9-14.5)	3.1 (0.6-3.7)	101.9 (90.1-108.4)	17.9 (15.1-30.3)
	P4b (n=4)	379.2 (333.9-416.3)	270.9 (230.9-330.5)	507 (443.5-538.2)	149 (119.7-254.7)	59.6 (54.3-74.8)	9 (7-11.7)	96.2 (92.5-100)	12.6 (11.8-13.3)	2.3 (0.7-4.1)	94.3 (86.3-96.4)	10.8 (6.5-18.2)
	P5b (n=2)	230.9 (210.7-251)	118.5 (103-134)	387.5 (327-448)	178.5 (129-228)	44.9 (38.2-51.5)	5 (1-9)	95 (95-95)	13.4 (13.3-13.4)	2 (1.4-2.6)	96.9 (94.8-99)	17.9 (13.4-22.5)
	p	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	0.23	0.12	0.67	0.69	0.69	0.60	0.33
> 200 /mm^3	P1c (n=24)	303.1	226	376.6	107.5	62.9	4.5	100	12.6	1.5	97.3	13
(c) (N=61)		(270.7-342.1)	(204.5-285.2)	(331.2-434)	(58.2-145.2)	(53.8-70.9)	(-0.7-8.5)	(97.5-100)	(11.7-13.4)	(0.6-2.5)	(93.1-101.6)	(9-20)
	P2c (n=26)	432.7 (403.5-483.6)	355.5 (318.7-404.2)	537 (478.5-593.2)	175 (137.5-274.2)	60 (48.3-66.1)	2.5 (-2-8)	100 (96.9-100)	12.2 (11.3-13.9)	2 (1.1-2.8)	99 (92.6-102.9)	16.9 (13.2-19.4)

Table 2. Contd.

	P3c (n=7)	661.5 (578-682.7)	504 (312-531)	821 (753-875)	460 (346-549)	60 (52.5-66.2)	1 (-2-3)	97.5 (95-100)	12.3 (11.7-14.2)	1.7 (0.1-3)	100.1 (95.5-105)	14.6 (11.8-19.9)
	P4c (n=4)	636.2 (556.8-756.9)	578 (449.7-641)	737 (696.7-925.7)	346 (237.2-445)	52.7 (49.1-61.9)	3.5 (1.2-6.5)	98.7 (93.7-100)	11.1 (8.6-12.5)	1.9 (0.3-3.8)	89.6 (83.5-90.4)	14.3 (10.6-15.9)
	p	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	0.33	0.64	0.62	0.28	0.91	**0.04**	0.56

p, Kruskal-Wallis test; IQR, interquartile range; Hb, hemoglobin.

below 100/mm^3, sex is explanatory of the partition of patients into five classes with a significant difference between these classes ($p < 0.05$). In each initial CD4 count category, the CD4 count meta-trajectory that looks most interesting is not attached to a class of patients with baseline features quite distinct from those of other classes.

Analysis of patient characteristics by MCA according to initial CD4 count category

Analysis of main medical follow-up characteristics

Patients with initial CD4 counts below 100/mm^3 have an average count of CD4 350/mm ^{3}, a Nadir CD4 350/mm^3 and a peak CD4 350/mm^3. These patients have a good adherence to treatment and are characterized by an absence of an alternative antiretroviral regimen. Overall, we noted that despite good adherence, the growth rate of CD4 is limited by the fact that they started treatment with very low CD4 counts and opportunistic infections. However, the average weight gain of these patients (>4.23 kg) indicates a medical treatment improvement. Patients whose initial CD4 count is between 100 to 200/mm^3, are characterized by an increase in hemoglobin count (> 2.22 kg), an average weight of 60 kg and an average weight gain of 4.23 kg. We noted in these patients who had been anaemic, a significant improvement in hemoglobin levels on antiretroviral therapy. Those with initial CD4 counts above 200/mm^3 presented these characteristics: average CD4 count >350/mm^3, nadir CD4 201/mm^3 and average CD4 peak >350/mm^3. We observed that beginning antiretroviral therapy with relatively high initial CD4 counts allows patients to maintain relatively high count of CD4, subject of course to good adherence. Their average CD4 gain (204.96/mm^3) is not necessarily disadvantageous since they begin treatment with initial CD4 count relatively higher than other patients do.

Analysis of the main baseline features

Patients with initial CD4 count below 100/mm^3 are generally male, not anaemic but with opportunistic infections at the initiation of treatment. Their initial CD4 cells percentage is below 15, which is more or less responsible for the lower CD4 count. Patients whose initial CD4 count is between 100 to 200/mm^3, are characterized by anemia, age lower or equal to 50 years and weighing less than 60 kg at the initiation of treatment. Those with initial CD4 counts above 200/mm^3 do not have opportunistic infections at initiation of treatment. The CD4 cells percentage is greater than or equal to 15, which is linked to the initial relatively high CD4 count.

DISCUSSION

Since the advent of highly active antiretroviral therapy, measurement of CD4 count level (Ledergerber et al., 1999) and especially the evolution of these levels in response to this treatment (Ledergerber et al., 1999; Chêne et al., 1998) are among the most prognostic variables of clinical progression. In our observational cohort, the analysis of meta-trajectories of immunological marker was used to study the determinants of these standard paths related to groups of patients treated with a nevirapine-based antiretroviral regimen in Abidjan, based on their initial CD4 count. This treatment with NVP has effectiveness comparable to that of treatment with a protease inhibitor in terms of immunological response (Wood et al., 2003). It is the first line treatment of choice in Côte d'Ivoire. It is judicious to detect, right from the initiation of treatment, the deleterious determinants of the evolution of immunological markers observed during therapeutic

monitoring in order to optimize the response to the nevirapine-based antiretroviral regimen. The objective of our study was to find the determinants collectively by groups of similar trajectories of CD4 counts and not individually. In general, according to the profile of meta-trajectories, CD4 cells gains are obvious during the first six months of treatment, and then afterwards their evolution varies according to class under nevirapine-based antiretroviral regimen regardless of initial CD4 count. Kitahata et al. (2002) have also noted best results in six months after initiation of highly active antiretroviral therapy at all levels of initial CD4 count. Other authors have shown that short-term efficacy of nevirapine-based treatment was equivalent to that of efavirenz-based regimen, and that the choice between the two NNRTIs could be based on their effectiveness at long term, their tolerance, their adherence, their cost or finally on their availability (Neuwelt et al., 2003). In each category of initial CD4 count, class of patients with lower initial CD4 count showed slower evolution of immunological markers during treatment. The immunological response to treatment is also more interesting in patients with an initial CD4 count greater than 200/mm^3. Patients with CD4 below 100/mm^3 with opportunistic infections at the initiation of treatment were characterized by good adherence. Therefore, despite a slower rate of evolution of CD4 counts they have improved certain medical parameters such as substantial weight gain. However, it should be noted that in these patients, weight gain and hemoglobin gain are highly variable according to the classes defined by the model. In all cases, substantial gains in CD4 counts were observed in several classes of patients with initial CD4 counts below 100/mm^3. Other authors have also shown the efficacy of nevirapine based antiretroviral regimen in terms of virological and immunological responses in very immunosuppressed naïve patients (initial CD4 count <100/mm ^{3}) (Lange, 2003; Manosuthi et al., 2004). This efficacy is equivalent to that obtained with efavirenz-based antiretroviral regimen (Manosuthi et al., 2004). In each category of initial CD4 count, the most interesting meta-trajectory showed two phases: an initial significant steep evolution of CD4, then a more gradual evolution in the second phase. Several authors have also shown that after the start of antiretroviral treatment for PLWAs, the increase of CD4 cells has a characteristic biphasic pattern. A steep initial phase probably reflects the redistribution of cells in the lymphoid tissue during the first months of treatment (Pakker et al., 1998; Bucy et al., 1999; Lederman et al., 2001; Diaz et al., 2003). Subsequently, the slope is decreasing, but the number of CD4 cells continues to increase at an average of 35 to 75/mm^3 per year, if viral suppression is maintained (Kaufmann et al., 2002; Hunt et al., 2003; Gulick et al., 2003; Viard et al., 2004; Smith et al., 2004a, b). However, analyses that separate the initial phase of growth in the number of CD4 cells may be necessary because different factors seem to influence this important initial slope (Hunt et al., 2003; Gulick et al., 2003). The initial CD4 percentage, in parallel with initial CD4 count, is also related to the immunological response of treatment. Indeed, an initial CD4 percentage greater than or equal to 15 is linked to higher initial CD4 count higher than 200/mm^3 with a significant evolution of CD4 count under treatment.

The presence or absence of opportunistic infections at treatment initiation influences the immunological response. Indeed in our study, patients with initial CD4 counts less than 100/mm^3 were particularly characterized by the presence of opportunistic infections in the early stage of treatment as opposed to patients with initial CD4 counts above 200/mm ^{3}. This study has generally highlighted the influence of certain characteristics on the immunological response of nevirapine-based anti-retroviral regimen in Côte d'Ivoire: initial CD4 count, initial CD4 percentage, adherence, presence or absence of initial opportunistic infections. One of the predictive factors of sustained viral response after the initiation of first antiretroviral therapy is the CD4 count at initiation of treatment (Yamashita et al., 2001; Moore et al., 2005, Garcia et al., 2004). An initial CD4 cells percentage less than 15 is considered to be at risk of opportunistic infections which must be considered, even though the CD4 count is higher than 200/mm^3 (Moore et al., 2005). The rate of treatment failure increases rapidly as adherence decreases (ANRS, 2001**)**. This failure can be correlated with changes in CD4 count by the definition of immunological failure (OMS, 2008). Another study determined the relation between adherence and immuno-virological response. The results showed real difficulties of adherence to antiretroviral therapy in Abidjan (Eholié, 2003). In addition, it is important to emphasize that adherence is necessary for optimum successful therapy. The problem of adherence is supported by a series of studies in Africa (Orrel et al., 2003; Tassie et al., 2003; Lanièce et al., 2003; Nachega et al., 2004; Daniel et al., 2004; Eholié et al., 2007), in which the lowest rate was observed in Côte d'Ivoire. Opportunistic infections are a very important clinical indicator in assessing the antiretroviral therapy response. They are related to the progression of the disease; their reoccurrence or their occurrence can be correlated to changes in CD4 counts. Even if body weight is not considered as a measure of effectiveness in theory, weight gain is still an element of satisfaction and encouragement for monitoring PLWAs. With symptomatic patients, the effectiveness of treatment results in an improvement in general condition with weight gain and loss of preexisting symptoms (Yeni, 2008) , as was the case in our study with patients with initial CD4 counts less than 100/mm^3. In the study entitled "Multicenter AIDS Cohort Study," Tarwater et al. (2001) noted that regardless of initial CD4 count, there was a significant increase in CD4 count during the first two years after starting HAART, followed by a stabilization between two and three and half years. This suggests the existence of a change in the slope of the trajectory of CD4 cells counts approximately two years after the start of treatment reaching a straight line. Our study on CD4 cells counts trajectories has been so important during those critical two years after initiation of treatment, in order to identify all factors that can limit this increasing trend of the immunological marker before its stabilization. Other authors have studied the change in long-term trajectories of CD4 counts with HIV-infected patients receiving antiretroviral therapy with a Bayesian random change-point model (Chu et al., 2005). The growth rates before the change in slope of the trajectories and timing of this change have been associated with initial CD4 count. Patients with low initial CD4 counts had a more rapid increase in CD4 from the onset and the point of gradient change trajectories occurred earlier compared with patients with initial CD4 counts higher. In this study, initial CD4 counts above 350/mm^3 are considered to be higher. In our study all patients had an initial CD4 count below 350/mm^3. This would suggest that they should all have a growth rate of CD4 cells during

these two years. That was not the case by analyzing the meta-trajectories of this immunological marker. Their modeling study has demonstrated the existence of a substantial interpersonal variation of CD4 count trajectory without highlighting possible causes that are linked. They just mentioned a possible difference in adherence among patients, especially women with initial CD4 count less than or equal to 100/mm^3, having a dramatic decline in CD4 after long-term stabilization. Our model showed a variation between groups of trajectories of CD4 counts linked to determinants. The NHD model has also shown its interest in predicting resuscitation in emergency with the analysis of the determinants of oximetry rates meta-trajectories (Petit, 2005) . It has been described as a new approach of data mining in many applications in humanitarian health (Prost and Petit, 2003).

Conclusion

Factors determining CD4 counts meta-trajectories profile during containing nevirapine-based antiretroviral regimen should be considered to optimize performance in the therapeutic monitoring of patients in Abidjan. The model of meta-trajectories of biomedical indicators provides a therapeutic decision support provided that we capitalize sufficient expertise for a better comprehension.

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