Available online at http://www.ifgdg.org

Int. J. Biol. Chem. Sci. 15(3): 881-888, June 2021

ISSN 1997-342X (Online), ISSN 1991-8631 (Print)

International Journal of Biological and Chemical Sciences

Original Paper http://ajol.info/index.php/ijbcs http://indexmedicus.afro.who.int

Kinetics of CD4+ T-cell recovery amongst HIV load suppressed patients on first-line antiretroviral therapy in Yaoundé, Cameroon

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Received: 30-01-2021 Accepted: 22-06-2021 Published: 30-06-2021

ABSTRACT

HIV infected patients on Antiretroviral Therapy (ART) are exposed to various immunological disorders. Immune reconstitution is one of the most challenging problem linked to morbidity and mortality in HIV patients. This study aimed at evaluating the kinetics of CD4+ T-cell recovery amongst HIV load suppressed patients on first-line ART in Yaoundé, Cameroon. This was a retrospective cohort study performed at the care and treatment units of the Yaoundé University Teaching Hospital and Essos Hospital Center, with viral suppressed patients initiated on ART between March and July 2015. Data were collected using a standard form and analyzed using R.3.6.2 software. A $p<0.05$ was considered statistically significant for a 95%CI. Of the 499 viral suppressed participants, 32% (n=160) were male and 68% (n=339) female; 33% and 40% had severe and moderate immunodepression at baseline, respectively; 9% and 28% remain respectively on the same immunological state. CD4+ T-cell count increased by 73%, 49% and 29% for patients that started treatment, with CD4+ <150 cells/ml, 150<CD4+<350 cells/ml and 350<CD4+<500 cells/ml, respectively and 14%, 34% and 40% reached a target of 500 cells/ml or more after 4 years of treatment. Elder patients and males were likely to have CD4+ T-cells less than 350 Cells/ml. Approximately 35% of patient started treatment with CD4+ T-cells <350 Cells/ml. CD4+ T-cells increased significantly during 4 years of treatment but, just 29% in average achieved CD4+ ≥ 500 cells/ml. CD4 T-cells recovery represent and important challenge in the immunological monitoring of long-term HIV infected patients on ART.

Keywords: Kinetic**,** CD4+ T-cells, HIV, Suppressed HIV load, ART

DOI : https://dx.doi.org/10.4314/ijbcs.v15i3.3

INTRODUCTION

HIV infection is linked to high mortality rates worldwide (Wang et al., 2016; Danforth et al. 2017) and especially in sub-Saharan Africa (Dwyer-Lindgren et al., 2019). Antiretroviral therapy (ART) leads to the maintenance of low or undetectable viral load, reduction of HIV transmission and the improvement and reconstitution of the immune system (Warren et al., 2019). The initiation on ART, followed by the significant declines of viral load leads to CD4+ redistribution and results in thymic activation (Rb-Silva et al., 2019). It has been shown that 15 to 30 percent of HIV infected individuals have suboptimal increase of CD4+ T-cells count, most commonly due to lack of compliance to ART. Some patients, because of the CD4+ T-cells recovery failure, will be at higher risk for adverse health outcomes (Darraj et al., 2018; Tough and McLaren, 2019). During the infection process, the virus replicates and induces a qualitative and quantitative CD4+ T-cells defects through several mechanisms (Okoye and Picker, 2013; Vidya Vijayan et al., 2017; Bonnet et al., 2019). The immune system responds by inducing the proliferation of T-cells subsets, with the aim to maintain their repertoire relatively constant during the infection stage (Porichis and Kaufmann, 2011; Okoye and Picker, 2013; Darraj et al., 2018; Bonnet et al., 2019). When at a certain point, the immune system cannot maintain the high rate of T-cell production sufficient to compensate the HIV-induced T-cells depletion, patients will develop AIDS related morbidity and mortality (Hsu et al., 2013; Pastor et al., 2018; Agosto and Henderson, 2018). Before the test and treat strategy implementation, CD4+ T-cell counts were used as the main indicator to consider the initiation of HIV infected patients on ART (Cameroon_National-Integrated-HIV-Guidelines, 2014). Now, in some resources limited settings (RLS), the follow-up of patients on ART is based on viral progression, despite the persistence of immune system activation related to non-AIDS diseases and mortality. The study aimed at evaluating the kinetic of CD4+ T-cell recovery amongst viral suppressed patients on first-line ART for four years (from 2015 to 2019) in Yaoundé, Cameroon.

MATERIALS AND METHODS

Study design

This was a retrospective cohort study performed at the care and treatment units of the Yaoundé University Teaching Hospital and Essos Hospital Center. The study population consisted of HIV infected patients on first-line ART. The enrolled participants were a cohort of patients initiated on ART between March and July 2015. The study was completed in July 2019.

All the HIV infected individuals on first-line ART were initially included. All the patients with unsuppressed viral load at baseline, those with suppressed viral load that become unsuppressed along the study period and those with non-consecutive documented HIV load and CD4+ T-cells for the period of the study, were excluded.

The first-line ART regimen according to the country guidelines were considered as follow: combination of two nucleoside reverse transcriptase inhibitors (NRTIs), chosen among Zidovudine (AZT), Tenofovir (TDF) and Lamivudine (3TC) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) being either Efavirenz (EFV) or Nevirapine (NVP). The suppressed HIV load patients were defined following the WHO classification as all the patients with HIV load less than 1000 copies per milliliter of blood (WHO, 2016).

Socio-demographics and clinical characteristics were collected at the same time with biological information of the patients retained in the cohort by using a standard form. The collected information included gender, age, treatment protocol, initiation date, CD4+ count and HIV load results. Administrative authorization from Hospitals' directors were obtained. Ethical clearance was obtained from

the Cameroon National Ethical committee (reference number 044/CNE/SE/2017) to carry out the study.

HIV load documented were obtained using the Cobas Ampli prep / Cobas Taqman 96 platform (Roche Diagnostics, Branchburg, New Jersey, USA), per manufacturer's instructions. The detection limit was <40 copies/ml. For CD4+ T-cells, the measurement was done based on the principle of immunophenotyping using the Pima reagent kit, and automated machine. Samples, including quality controls, were analyzed based on the manufacturers' guidelines.

Statistical analyzes

Data were analyzed using the R 3.6.2 software package (CRAN, R Core Team). Comparisons of CD4+ Tcells based on immune state and ART regimen were performed using the parametric student T-test by evaluating their means and interquartile range. The association between CD4+ Tcells and other variables were established using a logistic regression. The p <0.05 was considered statistically significant for a 95%CI.

RESULTS

Sociodemographic and clinical characteristics

A cohort of 499 viral suppressed participants was enrolled during the period of the study. 32% (n=160) were male and 68% (n=339) were female. At initiation on ART, 33% and 40% of those patients had severe and moderate immunodepression (CD4+<150 and 150<CD4+<350) respectively. Four years after they were linked to care, 9% and 28% still had severe and moderate immunodepression respectively. 14%, 34% and 40% of patients with CD4+<150 cells/ml, 150<CD4+<350 cells/ml and 350<CD4+<500 cells/ml respectively, reached a target of 500 cells/ml or more after 4 years of treatment (Table1).

Immune recovery for viral suppressed patients (VL<1000) taking Efavirenz and Nevirapine for 4 years

CD4+ T-cell counts increased by 73% (90 - 338 cells/ml), 49% (240 - 469 cells/ml) and 29% (407 - 552 cells/ml) for patients that started treatment with CD4+<150 cells/ml, 150<CD4+<350 cells/ml and 350<CD4+<500 cells/ml, respectively. There was a significant difference amongst patients in different immune state during the four years of treatment (Table 2). There was a significant difference amongst patients either on TDF+3TC+EFV and TDF+3TC+NVP during the four years of treatment. The difference was not significant between the two protocols. CD4+ T-Cells count increase by 41% (265 - 446 cells/ml), 52% (217 - 457 cells/ml), 50% (206 - 412 cells/ml) and 53% (199 - 424 cells/ml) for patients with the age range <30 years, 30 to 40 years, 40 to 50 years and >50 years respectively (Table 2).

Likelihood association between age, gender, regimen and CD4+ T-cells count after four years of treatment for n=499 participants

Women were likely to reconstitute their CD4+ compared to male with p= 0.006. Participants aged less than 30 years old and those aged more than 50 years old were likely to have CD4+ less than 350 Cells/ml, but that association was not statistically significant (Table 3).

Logistic regression between CD4+ T-cells, Gender, Sex, Viral load (VL), treatment and regimen

There was a significant association between CD4+ T-cells count and viral load (p=0.004, OR = 5.29, 95%CI = 2.16-14.27) and Gender (p=0.005, OR= 0.51, 95%CI= 0.32-0.82). The association with rupture of treatment, regimen, age, and regularity of treatment were not statistically significant (Table 4).

Table 1: Sociodemographic and clinical characteristics for the 499 HIV infected individuals.

Parameters	Modality	n (%)
Gender (n=499)	Male	160 (32%)
	Female	339(68%)
Regimen	TDF+3TC+EFV	400(80%)
	TDF+3TC+NVP	99(20)
Immune state at initiation (cell/ml)	CD4<150	167 (33%)
	150<CD4<350	201 (40%)
	350<CD4<500	77 (15%)
	CD4>500	54 (11%)
After 4 years (cell/ml)	CD4<150	45 (9%)
	150<CD4<350	139 (28%)
	350<CD4<500	134 (27%)
	CD4>500	181 (36%)
Virologic state (copies/ml)	VL<40	375 (75%)
	40 <VL< 1000	124 (25%)
Treatment interruption	Never	495 (98%)
	< 2 weeks	2 (1%)
	2 to 4 weeks	2 (1%)
	>4 weeks	0 (0%)
Reason for interruption	Negligence	1 (0.3%)
	Drug stock out	2 (1%)
	Others	1 (0.3%)
Age (median ±SD)	40±5 (22-68)	

Note: Efv: Efavirenz, NVP: Nevirapine, TDF: Tenofovir, 3TC: Lamivudine, VL: viral load, CD: clusters of differentiation, SD: standard deviation

Table 2: Immune recovery for viral suppressed patients taking Efavirenz and Nevirapine for 4 years.

Parameters	Modality	CD4 1st year	CD4 2nd year	CD4 3rd year	CD4 4th year	increased %	p value
		Median (range)					
Immune state (cell/ml)	CD4<150	90(6-149)	226(6-845)	310(3-931)	338(42-1001)	73	**p<0.001**
	150<CD4<350	240(152-350)	360(36-1160)	433(35-1133)	469(150-1480)	49	**p<0.001**
	350<CD4<500	407(350-499)	416(128-979)	540(52-1282)	552(203-1044)	29	**p<0.001**

	CD4>500	641(504-1527)	504(70-1862)	592(80-1921)	606(210-1549)	-5	**p=0.002**
Protocol	TDF+3TC+EFV	224(14-1124)	348.5(6-1862)	413.5(52-1921)	431.0(88-8114)	48	**p<0.001**
	TDF+3TC+NVP	180(6-1527)	332(6-1075)	417.5(3-1151)	484(42-1064)	63	**p<0.001**
Age (years)	<30	265(24-1527)	374(70-1086)	408(145-1921)	446(146-1004)	41	**p= 0.008**
	30 to 40	217(12-1124)	382.3(6-1160)	429.0(3-1151)	457.0(89-1480)	52	**p<0.001**
	40 to 50	206.0(6-1078)	327.0(36-1862)	441.0(35-1921)	412(80-8114)	50	**p<0.001**
	>50	199.0(14-809)	331.0(6-1043)	364.0(90-950)	424.0(88-1094)	53	**p<0.001**
Gender	Male	191.5(6-1527)	311.5(6-1036)	348.0(3-1921)	381.5(80-3441)	50	**p<0.001**
	Female	234.0(12-1099)	357.0(26-1862)	442.5(35-1282)	491.5(42-8114)	52	**p<0.001**

Note: Efv: Efavirenz, NVP: Nevirapine, TDF: Tenofovir, 3TC: Lamivudine, CD4: clusters of differentiation 4.

Table 3: Likelihood association between age, gender, regimen and CD4 T-Cells count.

Explanatory variables		**N**	**CD4<350**	**CD4>350**	**OR (95%CI)**	**p value**
Gender	Women	240	65(27.1)	175(72.9)	Reference	
	Men	112	47(42.0)	65(58.0)	0.51 (0.32-0.82)	**p=0.006**
Age (years)	<30	45	15(33.3)	30(66.7)	Reference	
	30 to 40	136	40(29.4)	96(70.6)	1.20 (0.57-2.44)	p=0.620
	40 to 50	106	37(34.9)	69(65.1)	0.93 (0.44-1.93)	p=0.852
	>50	65	20(30.8)	45(69.2)	1.12 (0.49-2.53)	p=0.777
Regimen	TDF+3TC+EFV	279	90(33.5)	179(66.5)	Reference	
	TDF+3TC+NVP	83	22(26.5)	61(73.5)	1.39 (0.81-2.45)	p=0.236

Note: Efv: Efavirenz, NVP: Nevirapine, TDF: Tenofovir, 3TC: Lamivudine, CD: clusters of differentiation.

Table 4: Univariable Logistic regression between CD4 T-cells and other variables.

Explanatory variable	**OR**	**95%CI**	**p-value**	**Model**
VL<1000 (copies/ml)	5.29	(2.16-14.27)	**0.004**	**CD4** = -0.76+1.66**VL**
age (years)	0.99	(0.97-1.02)	0.743	**CD4** = 0.91-0.003***Age**
Gender	0.51	(0.32-0.82)	**0.005**	**CD4** = 0.99-0.66***Sex**
Regimen	1.39	(0.81-2.45)	0.236	**CD4** = 0.6876+0.33***Molecule**
Regularity	4.41	(0.85-32.14)	0.089	**CD4** = -0.69+1.48***Reg**
Rupture oftreatment	0.57	(0.15-2.36)	0.416	**CD4** = 0.77-0.55***treatment Iinteruption**

Note: OR: regression coefficient, VL: Viral Load.

DISCUSSION

This was a retrospective cohort study with the aim to evaluate the kinetics of CD4+ T-cell recovery amongst viral suppressed patients on first-line ART for four years. It has been found that 33% and 40% of the patients had severe and moderate immunodepression at baseline respectively. 9% and 28% of those patients remain respectively on the same immunological state four years ago. This is highlighting the high rate of patients subject to immune disorders even though their viral load is less than 1000 copies/ml while starting treatment. Some authors (Lawn et al., 2006; Ahn et al., 2015; Pastor et al., 2018) found that HIV infection is follow by important immune phenomenon having a direct impact on T-cells subsets. Cytokine pro-inflammatory response cascade could be at the certain level responsible to the observed immune defect in some patients (Pastor et al., 2018). In many sub-Saharan settings, test and treat strategy has been put in place and patients are followed up using the viral load (Stafford et al., 2019). However, patients enrolled in ART with low CD4+ T-cells count have high risk of morbidity and mortality (Lawn et al., 2006; Danforth et al., 2017). Immunological nonresponse observed in this study might raise the concern about the immune follow up for patients on ART in resource limited settings.

It has also been realized that the CD4+ T-Cells count increased by 73%, 49% and 29% for patients that started treatment with CD4+<150 cells/ml, 150<CD4+<350 cells/ml and 350<CD4+<500 cells/ml respectively. The significant increase in CD4+ T-cells observed join the HIV treatment objective and it is well known that initiation of antiretroviral therapy has improved significantly the reconstitution of CD4+ T-cells with a low risk of associated advert disease effect (Tran et al. 2017; OARAC 2019). Although the increase of CD4+ T-cells, 14%, 34% and 40% of patients with CD4+<150 cells/ml, 150<CD4+<350 cells/ml and 350<CD4+<500 cells/ml respectively, reached a target of 500 cells/ml or more after 4 years of treatment. The most the patients start treatment with low CD4+, the most it is difficult for them to reach the immune competence. Some studies show that patients put on ART with CD4+ T-cells less than 200 cells/ml may have a weak immune recovery one and five years after treatment (Lawn et al., 2006; Ahn et al., 2015; Merci et al., 2017). The reconstitution was significantly associated to the protocol, gender and age. Young and elder patients were likely to have CD4+ T-cells less than 350 cells/ml. Previous studies have shown that some factors such as age, specific drug regimen, and initial CD4+ T-cells count have a significant impact on immune recovery among virological suppressed patients on antiretroviral therapy (Merci et al., 2017; Stirrup et al., 2018).

Some limitations are recognized for this study. It was difficult to get a complete immune profile markers and some clinical and infectious factors like co-infections, clinical stage, etc because of poor documentation.

Conclusion

This study shows that many patients (about 35%) infected by HIV were put on treatment while developing moderate immunosuppression. After four years of treatment, about 70% of patients were unable to reach the level of 500 cells/ml. CD4+ T-cells recovery is constituting a huge challenge in developing countries for the monitoring of HIV infected individuals and prevention of advert immune event like non-AIDS diseases.

COMPETING INTERESTS

All the authors of this paper declare no competing interests in this work.

ACKNOWLEDGEMENTS

The Yaoundé University Teaching Hospital and Essos Hospital Center.

AUTHORS' CONTRIBUTIONS

CHM, JMN and GMI: Development of research concept, data collection and analyzes, interpretation of results and participation in the initial draft of the manuscript. CMF, FAA, LMN, APNN, MCOA and GBJ: Development of research concept and drafting of manuscript. CRYD, MM: Contribution in the data

collection. All authors read and approved the final version of the manuscript.

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