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Long Term CD4 Count Increase in Routine Clinical Practice, Abidjan, Côte d'Ivoire

Souleymane DIABATÉ[1-3*], Fasséry DEMBÉLÉ[4], Serge-Olivier KOULÉ[4], Fatoumata KOFFI-KONÉ[4], Koné Soungalo épouse BAWA[4], Abdoulaye CISSÉ[4], Koffi Charles ANZAN[4], Éric DEMERS[1], and Michel ALARY[1,2,5]

[1]Axe Santé des populations et pratiques optimales en santé, Centre de recherche du CHU de Québec, Canada
[2]Département de médecine sociale et préventive, Université Laval, Canada
[3]Département d'infectiologie et santé publique, Université Alassane Ouattara, Côte d'Ivoire, West Africa
[4]Unité de soins ambulatoires et de conseils/Hôpital de jour (USAC), Abidjan, Côte d'Ivoire, West Africa
[5]Institut national de santé publique du Québec, Québec, Canada

***Corresponding author:** Souleymane DIABATÉ, Axe SP-POS, Centre de recherche du CHU de Québec, 1050 Chemin Sainte-Foy, G1S 4L8, Québec, Qc, Canada, Tel: 1-418-682-7511#82801; **E-mail:** dsouleym@hotmail.com

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Abstract

Background and objective: There are limited data on long term immune response to antiretroviral therapy delivered in routine conditions in sub-Saharan Africa. Accordingly, we conducted this retrospective cohort study to analyse long term immune response among HIV-positive patients receiving ART in routine clinical practice in Côte d'Ivoire.

Methods: The analyses included 2,568 adolescent and adult patients who initiated antiretroviral therapy between 1998 and 2013. CD4 count increase was estimated using generalized estimating equations for repeated measurements. Linear functions of the parameters based on the coefficients of linear contrast were used to estimate the slopes of CD4 gain.

Results: Almost 84% of the patients have received a Nevirapine or Efavirenz-based regimen at ART initiation. Median time (Interquartile range) under treatment was 3.44 (0.99–7.00) years and 34.6% patients were lost to follow-up. CD4 count increased consistently over time (p-value for linear trend<0.0001) and median cumulative increase (Interquartile range) was 509.4 (196.5–659.3) cells/mm^3 at month-144. Immune response was strong among patients starting ART with baseline CD4 counts ≤ 350/mm^3 and women. Overall, 132 patients underwent at least one episode of clinical and/or immunological failure. These episodes occurred mainly (53%) among severely immuno-depressed patients (0–100 CD4/mm^3). The overall crude mortality rate (95% Confidence interval) was 0.88 (0.71–1.06) per 100 person-years.

Conclusion: Sustained gains in CD4 count can be achieved in HIV-positive people remaining under care in routine clinical practice in sub-Saharan Africa.

Keywords: Antiretroviral therapy; HIV/AIDS; Immune response; Routine clinical practice; Sub-Saharan Africa

Introduction

Antiretroviral therapy (ART) has contributed to the decrease in HIV/AIDS-related mortality worldwide [1-3] and since the "3 by 5" initiative launched by the World Health Organisation (WHO) in 2003 [4], the number of HIV-positive people receiving ART has increased significantly in Africa [5]. However, close attention has to be paid to contextual factors which, along with limited resources devoted to national programmes of access to ART, have engendered specific problems such as recurrent stock-outs of drugs in the pharmacies, high rates of loss to follow-up, limited access to genotypic resistance testing and viral load monitoring with continued use of ineffective drugs or unnecessary switches to second line regimens [6,7]. Since the life expectancy of patients under treatment is increasing [8], these factors have to be considered as a Damocles sword able to impair the sustainability of immune reconstitution and to accelerate the development of resistant strains. Moreover, in sub-Saharan Africa where HIV transmission is predominantly heterosexual, an additional increase of the volume of people under ART is expected because of universal access to ART [9]. On that account, there is a need to continuously monitor the effectiveness of ART programmes scale-up and to report their specific problems in order to strengthen or adjust them, and to inform recommendations concerning issues like second line ART regimens, treatment as prevention and pre-exposure prophylaxis. Unfortunately, there are limited data on long term immune response to antiretroviral therapy delivered in routine conditions in sub-Saharan Africa [10-12]. In this retrospective cohort study, we report the results of CD4 cell count change over a period of twelve years of ART prescription in a public day-hospital in Abidjan, Côte d'Ivoire.

Methods

The "Unité de Soins Ambulatoires et de Conseils/Hôpital de jour" (USAC) is the largest HIV public day hospital dedicated to people living with HIV/AIDS in Côte d'Ivoire. It is located within the University Hospital Center of Treichville in Abidjan. It has a clinical and research vocation. In 1998, it was the sole day-hospital designated to participate, with few other medical centers, in a pilot project initiated by the Ivorian government with the support of UNAIDS in order to improve access to ART and AIDS care. In this study, were included 2,568 treatment-naive patients aged ≥ 15 years whose treatment was initiated at the "USAC" between October 1998 and June 2013. From 1998 to 2005, ART initiation criteria was ≤ 200 CD4/mm^3 or World Health Organization (WHO) clinical stage 4 irrespective of CD4 cell count and from 2006 to the end of the study it was ≤ 350 CD4/mm^3 or WHO clinical stage 3 or 4 irrespective of CD4 cell count [13]. Follow-up visits and provision of drugs were scheduled on a three-month interval basis. HIV treatment was provided free of charge since 2008. At each visit, patients reported the number of pills missed to their

clinician. Non adherent patients (>5% of the pills missed during the past three months) were referred to sociologists and social workers (adherence intervention). CD4 cell count was routinely performed every six months by means of flow cytometry. Patients had personal medical files where their clinical and biological information were recorded.

Statistical analyses

CD4 cell count change was estimated up to month-144 by means of generalized linear models with normal distribution and identity link using generalized estimating equations to take into account the dependency of observations due to repeated measurements. Linear functions of the parameters based on the coefficients of linear contrast were used to estimate the slopes of CD4 gain during the overall period. We analyse the slopes according to different variables including age, gender, first line ART regimens, adherence as assess by clinicians and CD4 cell count at baseline. Adherence to ART is treated as a time-dependent variable. The analyses were carried out on an intention-to-treat principle. We assessed absolute CD4 cell count at baseline and at month-144 as well as median time needed by patients to reach at least 500 CD4/mm^3. For these specific analyses, we used different cut-off points to determine adherence to ART (proportion of visits where a patient was classified as adherent=100%, ≥ 95%, ≥ 90%, and ≥ 80%) [14]. Kaplan-Meier survival curves with log-rank tests for unadjusted comparisons of subgroups (categorical variables) were obtained for the first clinical and/or immunological failure. We used Statistical Analyses System 9.3 (SAS Institute Inc., North Carolina, USA) for the statistical analyses.

Ethical consideration

Informed consent was not requested from patients because the data were collected in routine practice. However, consent to collect and analyze the data was obtained from the officials of USAC. The data were completely anonymized before they were analysed in this study.

Results

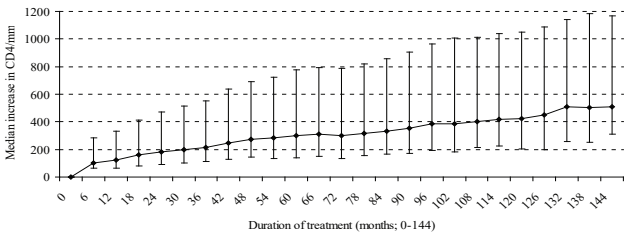
The majority of the patients were in their thirties at treatment initiation and women represented more than two-thirds of the sample (table 1). Men started ART with a more deteriorated immune system compared to women: median (Interquartile Range, IQR) baseline CD4 cell counts were 135 (46–238)/mm^3 in men and 168 (78–255)/mm^3 in women (table 2, p<0.005). The majority of the patients received a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based regimen at ART initiation (table 1). The proportion of patients who reported to their physician taking their drugs correctly varied from 99.8% at month-six to 89.7% at month-144. The analysis of adherence level over different time periods and the comparison of the periods before and after the beginning of drugs' provision for free in 2008 did not show significant variations according to gender and to immune recovery (data not shown). Median time (IQR) under treatment was 3.44 (0.99–7.00) years. The probability of remaining under treatment at month-24 was higher in women (77.7%) than in men (74%, p=0.028). Overall, 888 (34.6%) patients were lost to follow-up, with a higher frequency in men (38.1%) than in women (32.7%, p=0.006).

CD4 cell count change over time

The median gain in CD4 cell count/mm^3 increased with regularity form inclusion to month-132 (p-value for linear trend<0.005, figure 1). Stability was observed from month-132 to month=144. Overall, the median (IQR) cumulative increase was 103 (39.7–180), 212.4 (98.1–338.1), 301.9 (167.1–188), and 509.4 (196.5–659.3) cells/mm^3 at 6, 36, 72 and 144 months, respectively. Median (IQR) absolute CD4 cell count increased significantly from 157 (68–248) at baseline to 634 (400–825) at month-144 (table 2). Two patients out of five (39.7%) reached at least 500 CD4/mm^3 after a median (IQR) follow-up period of 26.8 (12.1–44.4) months. In general, the increase in CD4 cell count over time was much more significant among patients starting ART with baseline CD4 cell counts ≤ 350/mm^3 (table 3 and figure 2A). There was no overlapping between the 95% confidence intervals of the estimates for patients starting ART with the lowest (0-100 CD4/mm^3) and the highest (>350 CD4/mm^3) cell counts. The difference of slopes between both sub-groups remained unchanged after controlling for potential confounding variables including adherence kept in the

Variables	n (%) or median (IQR)
Age; median (Interquartile range, IQR) in years	37 (31–44)
Gender	
Female	1668 (65.0)
Male	900 (35.0)
CD4/mm^3	
0–100	867 (33.8)
101–200	734 (28.6)
201–350	696 (27.1)
>350	271 (10.5)
Period of treatment initiation	
1998-2005	
0-200 CD4/mm^3	728 (28.4)
201-350 CD4/mm^3	209 (8.2)
>350 CD4/mm^3	36 (1.4)
2006-2013	
0-200 CD4/mm^3	873 (34.0)
201-350 CD4/mm^3	487 (19.0)
>350 CD4/mm^3	235 (9.0)
CDC† clinical stage	
A	513 (20.7)
B	1485 (60.1)
C	475 (19.2)
Body mass index	
<18.5	565 (23.0)
18.5–24.9	1499 (61.2)
≥ 25	387 (15.8)
Antiretroviral regimen	
Nucleoside reverse transcriptase inhibitor (NRTIs)	108 (4.2)
Non-nucleoside reverse transcriptase inhibitor (NNRTIs)	2139 (83.9)
Protease inhibitors (PIs)	304 (11.9)
Median (IQR) duration on treatment (years)	3.44 (0.99–7.00)

Table 1: Baseline characteristics of HIV-positive people receiving antiretroviral therapy, Côte d'Ivoire, 1998–2013, N=2568
†Centers for Disease Control and Prevention; NRTIs, at least three of the following Abacavir, Didanosine, Lamuvidine, Stavudine, Tenofovir, Zidovudine; NNRTIs, at least two NRTIs plus Efavirenz or Nevirapine; PIs, at least two NRTIs plus one of the following Indinavir, Lopinavir, Nelfinavir, Saquinavir, and Ritonavir (boosted combinations)



Months	0	12	24	36	48	60	72	78	84	96	108	120	132	144
N	2568	1644	1392	1276	1168	980	825	746	663	381	241	196	118	59

Figure 1: Median (Interquartile range) increase in CD4 cell counts, Côte d'Ivoire, 1998-2013, N=2568 HIV-positive patients.
The median gain in CD4 cell count/mm^3 increased significantly form inclusion to year-12 (p-value for linear trend<0.0001).

adjusted model as a time-dependent variable. The gain for patients with higher initial CD4 cell count (>350/mm³) was notable in general, but it was not consistent over the entire period of observation as compared to other sub-groups (figure 2A). However, patients with elevated CD4 cell count at baseline were more likely to reach 500 CD4/mm³ within a shorter period of time compared to their counterparts (table 2). This was observed irrespective of the distribution of patients according to the period of treatment initiation (i.e. 1998-2005 or 2006-2013). Compared to men, immune response was more pronounced among women (p-value for the difference between slopes=0.007, figure 2B). This difference remained statistically significant in the adjusted model (table 3). Time needed to reach 500 CD4/mm³ was longer among men (table 2). On average (mean (± SD)), time between visits was longer in men than in women: (113.4 (± 151.4) versus 101.0 (± 89.6) days, p=0.031). Men also skipped more visits than women (0.47 versus 0.38 visit/year, p=0.049). There was no major difference in median CD4 cell count increase over time according to drugs' combinations at initiation (Protease inhibitor (PI)- versus non PI-based regimens, figure 2C), adherence (figure 2D) and for age (not shown). There was also no difference between 1998-2005 and 2006-2013 when the data were analysed over the first 84 months of follow-up (length of time between 2006 and 2013) (not shown). In comparison with their counterparts, median time needed to reach at least 500 CD4/mm³ was shorter for adherent patients and for those receiving non PI-regimen (table 2).

Time to first clinical and/or immunological failure, and mortality rates

One hundred and thirty-two (132) patients underwent at least one episode of clinical and/or immunological failure. The majority of these episodes (53%) occurred among severely immunodepressed HIV-positive subjects (0-100 CD4/mm³). Time to the first failure event was better for patients starting ART with higher CD4 cell count (figure 3) while it was similar regardless of gender (p-value from the Log-rank test=0.401), initial ART regimen (p=0.157) and age (p=0.197; data not shown).

Ninety eight (98) deaths were officially recorded in the medical records, for a total follow-up of 10890.85 person-years at risk. The overall crude mortality rate (95% CI) was 0.88 per 100 person-years (0.71–1.06) and

Variable | Category		Absolute CD4 count/mm³: median (IQR)		Median time (IQR) in months to reach at least 500 CD4/mm³
		Baseline	Month-144	
Overall		157 (68-248)	634 (400-825)	26.8 (12.1-44.4)
CD4/mm³	0–100	36 (13-69)	603 (396-710)	43.9 (29.4-63.9)
	101–200	150 (124-176)	662 (441-889)	27.9 (14.5-46.9)
	201–350	251 (226-285)	557 (354-769)	18.0 (10.8-31.6)
	>350	462 (396-570)	780 (574-1131)	14.4 (6.3-36.0)
Gender	Male	135 (46-238)	553 (224-728)	32.4 (15.3-52.6)
	Female	168 (78-255)	651 (419-877)	24.3 (12.0-41-5)
Adherence	Adherent[£]	156 (68-242)	660 (442-925)	23.7 (11.9-41.3)
	Non adherent	122 (45-221)	630 (349-738)	32.7 (18.0-58.1)
Treatment	PI-regimen	**124 (39-261)**	**599 (290-691)**	39.1 (17.9-58.0)
	Non PI-regimen	**159 (71-246)**	**706 (460-889)**	24.6 (12.0-42.1)
ART initiation criteria (1998-2005)[§]	0–200	**82 (27-140)**	**440 (284-633)**	39.6 (22.2-55.4)
	201-350[†]	**248 (226-275)**	**524 (341-764)**	18.1 (11.5-37.7)
	>350[†]	**412 (372-484)**	**753 (463-958)**	12.3 (7.2-26.4)
ART initiation criteria (2006-2013)[§]	0–200	**98 (37-151)**	**393 (231-566)**	28.3 (17.6-43.0)
	201-350	**255 (226-289)**	**580 (382-695)**	17.7 (9.1-29.9)
	>350[‡]	**470 (401-580)**	**958 (839-1077)**	14.2 (6.0-36.0)

Table 2: Absolute CD4 count and median time needed to reach at least 500 CD4/mm³ among HIV-positive treated patients, Côte d'Ivoire, 1998–2013 IQR: Interquartile range; PI: Protease inhibitor; [£]Patients who took their treatment correctly at least 80% of the time, similar results are obtained for cut-off points at 90%, 95% and 100%; [†]Symptomatic patients mostly: during that period ART initiation criteria was ≤ 200 CD4/mm³ or World Health Organization (WHO) clinical stage 4 irrespective of CD4 cell count; [‡]Symptomatic patients mostly: during that period ART initiation criteria was ≤ 350 CD4/mm³ or WHO clinical stage 3 or 4 irrespective of CD4 cell count; [§]Analyses from month-0 to month-84 instead of month-144 to account for the length of the second period (2006 to 2013); In bold, differences between baseline and last measure not statistically significant across categories.

Model	Bivariate model				Adjusted model[†]			
Variables	β	SE	P value	95% CI	β	SE	P value	95% CI
Baseline CD4/mm³								
0–100 (slope a)	22.11	0.99	<0.0001	20.17-24.05	20.87	1.16	<0.0001	18.60-23.14
101–200 (slope b)	20.26	1.19	<0.0001	17.92-22.59	17.01	1.29	<0.0001	14.49-19.54
201–350 (slope c)	19.19	1.66	<0.0001	15.93-22.44	18.33	1.82	<0.0001	14.76-21.90
>350 (slope d)	14.56	2.69	<0.0001	9.29-19.82	12.97	3.35	0.0010	6.40-19.54
Slope a minus slope d	7.55	2.86	0.0151	1.94-13.16	7.90	3.54	0.0352	0.96-14.85
Slope b minus slope d	5.70	2.94	0.0641	-0.06-11.46	4.04	3.57	0.2657	-2.95-11.04
Slope c minus slope d	4.63	3.16	0.1540	-1.56-10.82	5.37	3.81	0.1687	-2.10-12.83
Gender								
Female	22.07	0.91	<0.0001	20.29-23.85	19.60	1.18	<0.0001	19.60-21.92
Male	18.37	1.03	<0.0001	16.36-20.39	16.00	1.43	<0.0001	15.00-17.81
Gender difference	3.70	1.37	0.0071	1.01-6.39	4.60	11.58	0.0037	4.60-7.71

Table 3: Estimation of CD4 cell count slopes over time and comparison of sub-groups according to baseline CD4 cell count and gender, Abidjan, Côte d'Ivoire; 1998-2013; N=2568 treated HIV-positive patients [†]Adjusted for baseline age, body mass index, Centers for Disease Control and Prevention clinical stage, chemoprophylaxis with Cotrimoxazole, school attendance, and for adherence treated as a time-dependent variable (adherent patients are those who reported to their physician taking their drugs as prescribed); β=effect estimate; SE=standard error; 95% CI=95% confidence interval

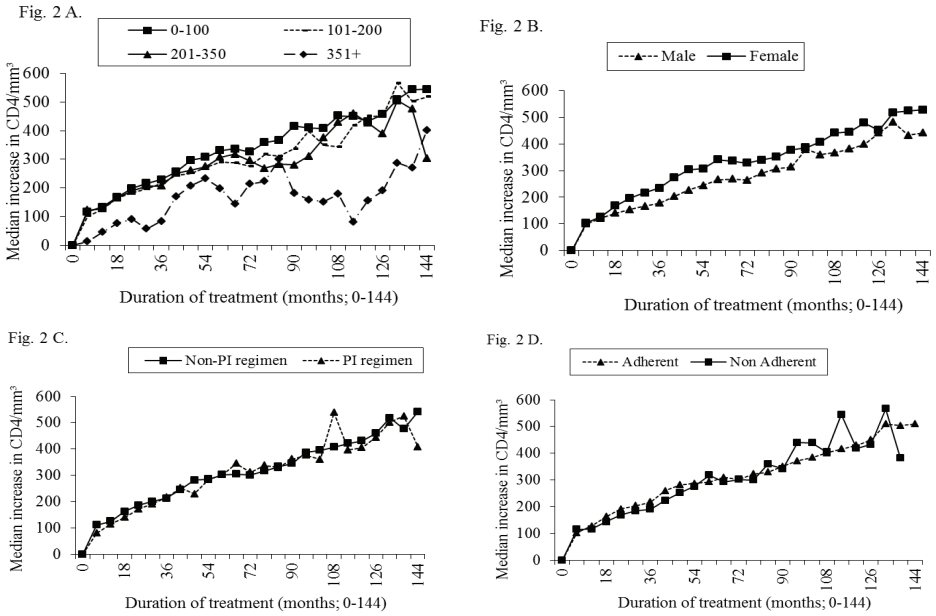


Figure 2: Median increase in CD4 cell counts according to baseline levels and gender, first line treatment and adherence, Côte d'Ivoire, 1998-2013, N=2568 HIV-positive patients.
For all four slopes, P values for linear trend<0.0001. **2A.** P value for differences between groups=0.0423; **2B.** P value for gender differences=0.0071. **2C.** P value for differences between first line treatments (intention to treat principle)=0.0628; **2D.** At each visit, adherent patients are those who reported to their physician taking their drugs as prescribed. P value for differences between adherent patients and their counterparts=0.976.

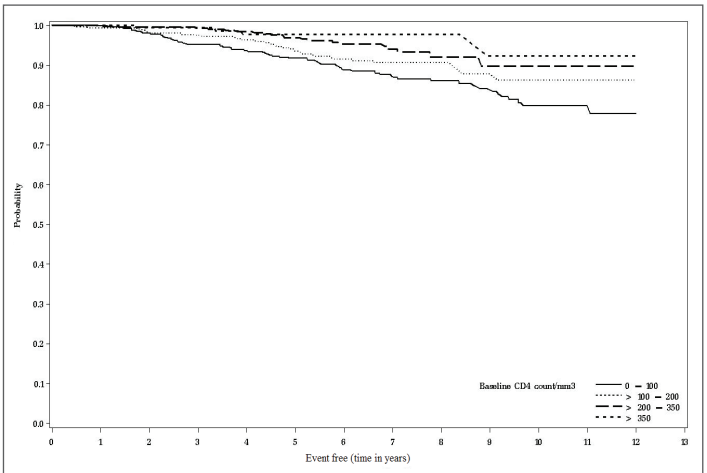


Figure 3: Time to the first clinical and/or immunological failure according to baseline CD4 cell count, Côte d'Ivoire, 1998–2013, N=2568 HIV-positive patients.
P-value for sub-group comparisons (Log-Rank test)=0.0003

it decreased with increasing CD4 cell count at ART initiation (data not shown). There was no statistically significant difference in mortality according to ART regimen, gender and age (data not shown).

Discussion

The main result of this study is the long term improvement in CD4 cell count. Twenty-five percent of the patients were followed for at least seven years. There are scarce results reporting positive CD4 count slopes during such a long period in routine practice conditions in sub-Saharan Africa. Strong gains have already been reported in Africa, but, over shorter periods of follow-up [10-12,15]. In this study, there were some differences in CD4 cell gain over time according to baseline levels (figure 2A). This was due principally to a less pronounced and inconsistent response in patients who initiated ART at higher CD4 counts (350+/mm^3) in comparison with those who were enrolled with a profound immunodeficiency (≤ 100 CD4/mm^3). The consistency of this differential evolution observed across continents [16-18] is rather in favour of a ceiling effect [19] than in favour of better adherence behaviour among more immuno-depressed people initiating ART. Indeed, CD4 cell gain under treatment is expected to be less significant among patients with elevated baseline counts because they are much closer to the physiological equilibrium. This assumption is in line with the fact that in spite of a less pronounced response, median time needed to reach at least 500 CD4/mm^3 was shorter among patients who initiated ART with more CD4 cells. In consistency with these results, previous studies have shown that patients starting treatment with >200 CD4/mm^3 were more likely to achieve normal levels during follow-up [10,12]. The relatively limited number of patients has certainly contributed to the fluctuations observed over time in the sub-group with elevated baseline CD4 cells.

During the first few years of follow-up, the slopes were identical according to gender and, thereafter, there was a better response in women (figure 2B, p=0.007). The difference was maintained till the end of the period of observation. Research on the relationship between gender and response to ART has generated divergent results. Ours are in disagreement with some [20,21] and in agreement with others [17,22,23]. As women started to achieve better immune response about two years after ART initiation, baseline CD4 cell counts are unlikely to have contributed to this gender difference in immune reconstitution. If that difference was due to baseline differences in CD4 cell count it would have been likely observed earlier as in figure 2A where we can see earlier differences in immune response according to baseline levels. In addition, based on the ceiling effect, better response was expected among men because they started ART with a more pronounced immunodeficiency. Hence, the delayed contrast of the slopes between men and women can be attributed to a paradoxical relationship between health status improvement over time and persistence under treatment, particularly among men. Timeliness of clinic attendance that has been found to predict virological response and

drug resistance in Africa and Asia [24] could have been unsatisfactory among men, especially, after improvement of their quality of life under treatment. Indeed, because of a relatively deteriorated health status and comprehensive adherence sessions animated by sociologists and social workers at the medical center, both men and women seeking treatment may be more motivated to take correctly their pills and to respect the scheduled visits during the first months of treatment. However, enhancement and evidence of positive health outcomes may, thereafter, lead men to skip or postpone scheduled visits more frequently than women. We observed higher rates of visits' skips and losses to follow-up as well as longer periods of time between visits among men. Our results are in accordance with previous ones showing a better treatment seeking behaviour among women [25] and a worse attendance at follow-up visits by men [17]. In addition, in qualitative interviews, return to a normal life has already been described as a key reason for loss to follow-up [26].

In our study, adherence did not vary according to gender and it was not associated with a better immune response. This could be due to the fact that adherence was not assessed in a standardized way. However, if gender issues can induce differences in adherence to ART as such, so far a consistent link has not been found between both factors in quantitative studies in Africa [27]. Also, since adherence is investigated by clinicians, both women and men may tend to overestimate it in order to maintain a supportive relationship with health care providers. Over-reporting bias is common with adherence self-reports [28]. Absence of a better median increase in CD4 cell count among adherent patients may also be related to higher levels of absolute CD4 cell count at baseline compared to non adherent patients. This hypothesis in supported by the shorter period of time needed to reach at least 500 CD4/mm^3 among adherent patients. There was no accurate data to identify all the reasons related to poor adherence, but it should be noted that during the study period pharmacies were confronted in Côte d'Ivoire with drug stock-outs [29]. A sizeable number of unplanned changes of drug combinations by clinicians and of treatment interruptions by patients were due to those stock-outs [29].

The type of the initial ART regimen (PI-based or not) did not distinctively impact immune response (figure 2C). Over the whole period, both slopes were much the same. This result is in favour of the effectiveness of Triomune® (stavudine+lamuvidine+nevirapine; Cipla, Mumbai, India) that was the main non-PI based first line regimen during more than a decade in many resource-constrained countries including Côte d'Ivoire [30]. Previous results have shown the efficacy of this generic fixed-dose combination [31]. Due to numerous side effects like peripheral neuropathy, lipodystrophy and metabolic complications related mainly to Stavudine, this cheap and easy-to-take triple combination has recently been removed from first line options in accordance with WHO recommendations [30]. Longer duration before reaching at least 500 CD4/ mm^3 among patients receiving PI-regimen derives in part from the fact that those drugs were restricted to patients with advanced HIV infection. Even though previous studies have reported that immune recovery diminishes in parallel with the thymus gland function that, in turn, lessens with increasing age [32,33], we and others [34,35] did not find a relationship between immune response and age. This discrepancy may be attributable to the fact that our study population was relatively young. Median (IQR) age was 37 (31–44) years.

Viral load was not routinely monitored during the study period. This is why we have reported results on clinical and/or immunological failure only, even though they are known to be poor predictors of virological failure and to result in accumulation of resistance or in unnecessary switches to second line ART [36]. As anticipated, patients with a better immunological status at ART initiation had a lower risk of clinical and/or immunological failure [37] and they also had a lower mortality rate [38]. The overall low mortality rate in this study should be interpreted with caution since we did not correct for loss to follow-up. Loss to follow-up was elevated. A review of 32 publications from 13 sub-Saharan African countries shows that only 60% of the patients remained under care two years after ART initiation [39]. Taking into account loss to follow-up would have probably resulted in a less pronounced immune recovery. The strong response of the immune system to ART among patients remaining under care in this study indicates the imperious necessity to develop effective interventions aiming at reducing loss to follow-up rates in national programmes for access to ART in sub-Saharan Africa.

Absence of standardization during the collection process and paucity of data related to side effects, opportunistic infections and virological treatment failure did not allow us to analyse in depth these issues.

Conclusion

The results of this retrospective study conducted in routine clinical conditions in a resource limited setting are encouraging since they show that HIV-positive people remaining under care can achieve substantial gains in CD4 cell counts whatever the baseline levels are. With the increase in life expectancy of treated patients, interventions to reduce losses to follow-up are needed.

Conflicts of Interest

This article content has no conflict of interest.

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