Influence of lifelong cumulative HIV viremia on long-term recovery of $CD4^+$ cell count and $CD4^+/CD8^+$ ratio among patients on combination antiretroviral therapy

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Objective: We explored the impact of lifelong cumulative HIV viremia on immunological recovery during antiretroviral therapy, according to the timing of treatment initiation.

Methods: We estimated lifelong cumulative HIV viremia in patients followed in the ANRS PRIMO cohort since primary infection, including 244 patients who started treatment during PHI and had at least one treatment interruption, and 218 patients who started treatment later but with no interruptions. The impact of cumulative viremia on current immunological status was analysed using linear and logistic regression models.

Results: At the last visit on treatment, median $CD4^+$ cell count was 645 cells/μl in the early/intermittent treatment group (median time from infection 9.5 years, 4.8 years of continuous treatment since last resumption), and 654 cells/μl in the deferred/continuous treatment group (median time from infection 6.1 years, 3.0 years of continuous treatment). Only 36.1 and 39.8% of patients achieved a $CD4^+/CD8^+$ ratio of more than 1, respectively. Current $CD4^+$ cell count was not associated with cumulative HIV viremia in either group. In contrast, patients with high cumulative HIV viremia (>66th percentile vs. <33rd percentile) were less likely to achieve a $CD4^+/CD8^+$ ratio of more than 1 (26.8 vs. 43.3%, $P = 0.003$), even after controlling for the baseline $CD4^+/CD8^+$ ratio, treatment duration, sex and age. Much higher $CD4^+$ cell count and $CD4^+/CD8^+$ ratio were reached in early/continuous treatment, that is low viremia exposure group.

Conclusion: Our results underline the critical need in early-treated patients to maintain adherence, in order to limit cumulative HIV viremia and optimize immunological recovery, notably the $CD4^+/CD8^+$ ratio.

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Introduction

The primary phase of HIV infection (PHI) is a period associated with intense viral replication. Early treatment reduces the duration of exposure to high-level viremia. Guidelines for treatment initiation during PHI have evolved over time. In France, in clinical practice, treatment used to be started in all patients presenting during PHI [1], until specific guidelines issued in 2002 recommended treatment initiation only in case of symptomatic primary infection or a low $CD4^+$ cell count [2]. Moreover, in the early era of combination antiretroviral therapy (cART), because of concerns regarding toxicity, PHI treatment was recommended for 18–24 months only. Treatment interruption has not been recommended since 2008. More recently, as in the USA, a continuous treatment has been recommended at diagnosis, regardless of the stage of HIV infection, since 2013 [3,4]. Apart from the framework of clinical trials or of past recommendations, treatment interruptions can still occur nowadays, because of patient decisions, suboptimal adherence or irregular follow-up. In the vast majority of cases, viremia rapidly rebounds after discontinuation of cART [5–12].

The impact of cumulative exposure to HIV viremia is a growing focus of attention. Estimates of lifelong exposure to HIV viremia must take into account both the degree of viremia and the duration of each viremic episode since HIV infection, and relevant methods were proposed a few years ago [13,14]. In the pre-cART era, cumulative HIV viremia among untreated patients was reported to influence the risk of AIDS and death, independently of the time since infection, age, race, the $CD4^+$ cell count and viral load [14]. In patients on cART, high cumulative HIV viremia was found to be predictive of the risk of developing AIDS-related lymphoma [13] and all-cause mortality [15,16]. In young adults infected perinatally with HIV, with currently controlled viral replication, the main factor associated with current total cellular HIV-DNA load was cumulative viremia over the previous 5 years [17]. The only study to evaluate the impact of cumulative HIV viremia on $CD4^+$ cell count gain in treated patients showed no significant relationship [18]. However, in this study, only exposure to cumulative HIV viremia from cART initiation was analysed and not the lifelong cumulative viremia.

To what extent the sum of past exposure to the virus since HIV infection affects immunological recovery on treatment in terms of the $CD4^+$ cell count and the $CD4^+/CD8^+$ ratio has rarely been explored. Low $CD4^+/CD8^+$ ratio has been shown in recent studies to be associated with immune activation and higher morbidity, more specifically non-AIDS related events [19,20]. The increase in $CD4^+/CD8^+$ ratio is therefore to be considered along with the $CD4^+$ cell count gain in the optimal response to treatment.

It is not known whether cumulative exposure to viremia is more deleterious for long-term immune recovery when treatment initiated during PHI is discontinued or when treatment is deferred.

Using data from the French ANRS Primo Cohort, a large cohort of patients followed since primary HIV infection, we analysed the influence of cumulative HIV viremia since HIV infection on current immunological status, according to the timing of cART initiation.

Materials and methods

The ANRS PRIMO cohort

The ANRS PRIMO cohort (CO06) is an ongoing prospective cohort created in 1996. Patients are enrolled during primary HIV infection, defined by an incomplete western blot, or detectable p24 antigenemia/plasma viral load with a negative or weakly reactive ELISA, or an interval of 6 months or less between a negative and positive ELISA test.

$CD4^+$ cell count, $CD8^+$ cell count and plasma viral load data are recorded along with clinical characteristics, first at enrolment and then during follow-up visits (M1, M3, M6 and subsequently every 6 months). Data are regularly monitored, and all clinical AIDS events are authentified.

Study population

Among the 586 patients who started cART (at least three drugs) during PHI (within 3 months after HIV infection), we selected the 244 patients who had had at least one treatment interruption (>15 days), whatever the reason, and who were back on treatment before the last follow-up visit (Fig. 1). This group represents patients with lifelong viremia mostly accumulated after treatment interruption. Among the 248 patients in whom treatment was deferred for at least 12 months after infection, we selected the 218 patients who pursued treatment with no interruptions greater than 15 days and still were on treatment at the last follow-up visit. This group represents patients with lifelong viremia mostly accumulated between HIV infection and treatment initiation at the chronic stage.

For purposes of comparison with a group with very low cumulative viremia exposure, we also analysed current $CD4^+$ and $CD4^+/CD8^+$ ratio in the 265 patients who initiated treatment during PHI and did not interrupt treatment (early/continuous group).

Statistical analysis

Cumulative HIV viremia was calculated according to Zoufaly *et al.* [13], by summing over the whole period the products of the log viral load and the time interval extending to the previous measurement; this time interval

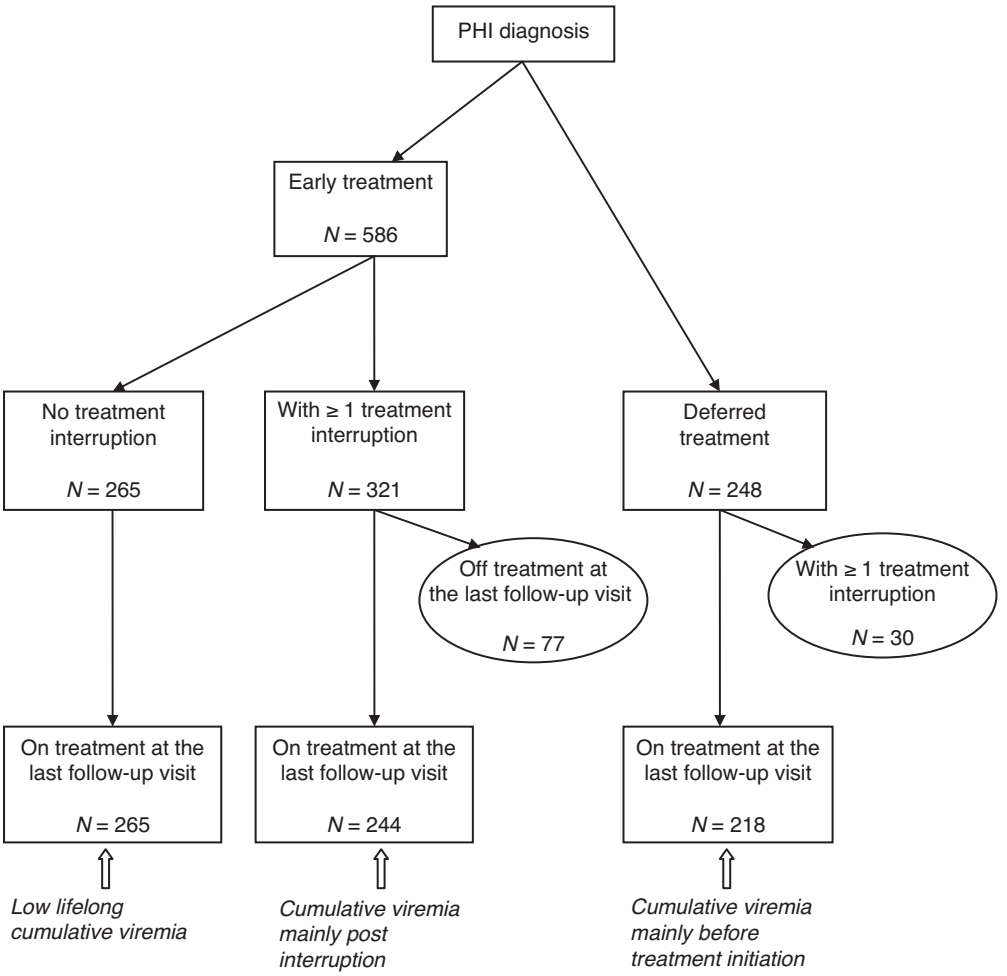

Fig. 1. Flow chart of the study.

was set to a maximum of 180 days when the previous viral load measurement was more distant. For the first viral load measured at enrolment during primary infection, the time interval was extended to the estimated date of HIV infection. Only viral load measurements recorded at the protocol visits, hence at identical scheduled time intervals for all the patients, were used in the calculation. The detection limit of HIV-RNA quantification assays evolved over time. Over the whole study period, the highest detection limit was 400 copies/ml, and we therefore included only viral load values above this threshold; all the protocol viral load measurements were considered, whether the patient was on or off cART. We performed a sensitivity analysis considering a threshold of 50 copies/ml instead of 400 copies/ml, wherein all values undetectable at a threshold of more than 50 copies/ml were considered as undetectable at a threshold of 50 copies/ml.

The outcome measure was immunological status at the last cohort follow-up visit on treatment, referred to below as 'current' status. We analysed the current $CD4^+$ cell count and the current $CD4^+/CD8^+$ ratio as continuous variables, and the following binary outcomes, considered to reflect an optimal treatment response: $CD4^+$ cell count more than 500 cells/μl and a $CD4^+/CD8^+$ ratio more than 1.

To assess the influence of cumulative HIV viremia on each of these outcomes, four different multivariate analyses were performed with cumulative viremia as the independent variable, categorized by its tertiles. To better characterize the dose–relationship between cumulative HIV viremia and current immunological status, cumulative viremia was also entered in an alternative multivariate model as a function of the restricted cubic spline with three knots (located at the fifth, 50th and 95th percentiles) [21]. The influence of cumulative HIV viremia on the current $CD4^+$ cell count and $CD4^+/CD8^+$ ratio was examined using linear regression models. Its impact on the probability of an optimal treatment response ($CD4^+$ cell count >500 cells/μl or $CD4^+/CD8^+ >1$) was examined with logistic regression models. In all models, we chose to adjust for baseline immunological parameters ($CD4^+$ cell count or $CD4^+/CD8^+$ ratio) at PHI diagnosis and not at cART

initiation, as the latter might lie in the causal pathway between cumulative HIV viremia and outcome. The other adjustment variables were sex, age at cART initiation and the cumulative treatment duration, or the duration since last resumption.

Statistical analyses used SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Characteristics of the patients and long-term therapeutic response

The analysis included patients who were on treatment at the last follow-up visit, of whom 244 received early/intermittent treatment, 218 received deferred/continuous treatment and 265 received early/continuous treatment (Fig. 1). In the first group, cART was started a median of 38 days after HIV infection, at a median $CD4^+$ cell count of 471 cells/μl (Table 1). These patients' median follow-up after cART initiation was 9.5 years. The first treatment interruption occurred after a median of 14.6 months of treatment, at a median $CD4^+$ cell count of 681 cells/μl and a median $CD4^+/CD8^+$ ratio of 0.97. They had one (52.5%) or several (47.5%) treatment interruptions. The median cumulative duration of the interruptions was 2.5 years, and the median $CD4^+$ cell count at the last treatment resumption was 355 cells/μl. At the last follow-up visit, the median $CD4^+$ cell count was 645 cells/μl, after a median of 4.8 years of continuous treatment since the last resumption; a median of 72.8% of the time since HIV infection had been spent on treatment. The $CD4^+$ cell count at the last cohort follow-up visit was more than 500 cells/μl in 75% of patients; the $CD4^+/CD8^+$ ratio was more than 1 in only 36.1% of patients, 96% of whom had $CD4^+$ cell count more than 500 cells/μl.

Compared with the patients who started treatment during PHI, the 218 patients in whom treatment was deferred had significantly higher $CD4^+$ cell counts and lower plasma viral loads at PHI diagnosis ($P < 0.0001$), and were also less likely to have had a symptomatic PHI (82.1 vs. 90.2%, $P = 0.01$). They started treatment a median of 30.2 months after HIV infection. Their median $CD4^+$ cell count at cART initiation was 336 cells/μl overall, but gradually increased during the study period, from 259 cells/μl in 2002–2003 to 379 cells/μl in 2010–2011, along with the evolution of French guidelines [1]. At the last follow-up visit, the median $CD4^+$ cell count was 654 cells/μl, a median of 6.1 years after HIV infection and after a median of 3.0 years of continuous treatment; 54% of the time since HIV infection had been spent on treatment. The $CD4^+$ cell count at the last follow-up visit was more than 500 cells/μl in 76.2% of patients and the $CD4^+/CD8^+$ ratio was more than 1 in only 39.8% of patients.

Current plasma HIV-RNA was less than 50 copies/ml in 85.1% of patients in the early/intermittent treatment group and 84.3% in the deferred/continuous group, $P = 0.8$, and the current treatment regimen was similar in the two groups. Twelve patients (4.9%) in the early/intermittent group and 11 patients (5.1%) in the deferred/continuous group experienced an AIDS-defining event during follow-up. In the early/intermittent group, the first AIDS event occurred a median of 56.2 months [interquartile range (IQR) 30.8–64.6] after treatment initiation, either during or after a treatment interruption, except for one patient who developed a cutaneous Kaposi disease early after infection (3.4 months). The events were tuberculosis ($n = 2$), Kaposi's disease ($n = 5$), pneumocystis pneumonia ($n = 3$), lymphoma ($n = 1$) and toxoplasmosis ($n = 1$). In the deferred/continuous group, eight events occurred before cART initiation and three after a median of 13.3 months on cART. The events were Kaposi's disease ($n = 3$), pneumonia ($n = 1$) pneumocystis pneumonia ($n = 2$), lymphoma ($n = 3$), cytomegalovirus retinitis ($n = 1$) and cryptosporidiosis ($n = 1$). The median $CD4^+$ cell counts at the time of these events were 345 cells/μl (IQR 205–414) in the early/intermittent group and 283 (IQR 173–462) in the deferred/continuous group.

Influence of cumulative HIV viremia on current immunological status

The median cumulative HIV viremia to which patients had been exposed since HIV infection was 9.9 years*$\log_{10}$ copies/ml in the early/intermittent treatment group, in which the median cumulative time off treatment was 2.7 years. Cumulative HIV viremia was similar in the deferred/continuous treatment group (median: 9.5 years*$\log_{10}$ copies/ml), who started treatment a median of 2.4 years after HIV infection. Cumulative HIV viremia correlated negatively with the percentage of the time since infection spent on treatment (Spearman rank correlation $r = -0.71$, $P < 0.0001$, and $r = -0.58$, $P < 0.0001$ in the early and deferred treatment groups, respectively).

The current $CD4^+$ cell count at the last follow-up visit was not significantly associated with cumulative HIV viremia in either treatment group (Table 2). Current $CD4^+$ cell count was positively associated with both the $CD4^+$ cell count at PHI diagnosis and with the cumulative duration of treatment in both groups, and also with younger age at cART initiation in the deferred treatment group only. The lack of association between the current $CD4^+$ cell count and cumulative HIV viremia persisted after controlling for the duration of the latest treatment period rather than for the total duration of treatment. Similar results were obtained when the $CD4^+$ cell count outcome was more than 500 or more than 800 cells/μl.

In contrast, a significant association was found between cumulative HIV viremia and the current $CD4^+/CD8^+$

Table 1. Patients and treatment response according to the treatment timing: the ANRS PRIMO cohort.

	Early/intermittent treatment, $N=244$	Deferred/continuous treatment, $N=218$	P
Women	18.0% (44)	14.2% (31)	0.3
Age at HIV infection, years	35.8 (30.4; 44.8)	35.9 (30.0; 42.9)	0.4
At enrollment			
$CD4^+$ cell count (cells/μl)	471 (326; 602)	554 (447; 704)	<0.0001
$CD8^+$ cell count (cells/μl)	1011 (689; 1536)	1009 (710; 1396)	0.6
$CD4^+/CD8^+$ ratio	0.41 (0.24; 0.66)	0.58 (0.39; 0.86)	<0.0001
HIV-RNA, $\log_{10}$ copies/ml	5.4 (4.9; 5.9)	4.8 (4.1; 5.3)	<0.0001
At cART initiation			
Time from HIV infection (months)	1.3 (1.1; 1.6)	30.2 (19.8; 48.5)	<0.0001
$CD4^+$ cell count (cells/μl)[a]	471 (326; 600)	336 (267; 410)	<0.0001
$CD8^+$ cell count (cells/μl)[a]	1008 (686; 1531)	930 (663; 1185)	0.004
$CD4^+/CD8^+$ ratio[a]	0.42 (0.24; 0.67)	0.36 (0.28; 0.50)	0.11
HIV-RNA, $\log_{10}$ copies/ml[a]	5.4 (4.9; 5.9)	4.8 (4.2; 5.2)	<0.0001
At first cART interruption			
Time from cART initiation, months	14.6 (8.4; 24.5)		
$CD4^+$ cell count (cells/μl)[a]	681 (520; 910)		
$CD8^+$ cell count (cells/μl)[a]	692 (526; 932)		
$CD4^+/CD8^+$ ratio[a]	0.97 (0.71; 1.37)		
HIV-RNA <50 copies/ml[a]	76.8% (179)		
Number of treatment interruptions	1 (1;3)		
At last cART resumption			
Time from HIV infection, months	59.0 (37.4; 84.5)		
$CD4^+$ cell count (cells/μl)[a]	355 (289; 472)		
$CD8^+$ cell count (cells/μl)[a]	952 (664; 1300)		
$CD4^+/CD8^+$ ratio[a]	0.38 (0.27; 0.57)		
HIV-RNA ($\log_{10}$ copies/ml)	4.5 (3.8; 5.0)		
Follow-up after cART initiation (years)	9.5 (8.0; 12.4)	3.0 (1.8; 4.5)	<0.0001
At last follow-up visit			
Time since HIV infection (years)	9.7 (8.1; 12.6)	6.1 (4.6; 7.8)	<0.0001
Cumulative treatment duration (years)	6.5 (4.3; 8.9)	3.0 (1.8; 4.5)	<0.0001
Duration of last cART (years)	4.8 (2.5; 6.6)	3.0 (1.8; 4.5)	<0.0001
Percentage of time on treatment	0.7 (0.5; 0.9)	0.5 (0.4; 0.7)	<0.0001
Nadir $CD4^+$ cell count (cells/μl)	295 (231; 364)	309 (246; 373)	0.16
Cumulative HIV viremia[b]	9.9 (5.7; 15.9)	9.5 (6.4; 14.9)	0.7
Current treatment			0.7
PI or PI/r-based regimen	46.7% (114)	48.2% (105)	
NNRTI-based regimen	42.6% (104)	43.6% (95)	
Other	10.7% (26)	8.3% (18)	
Current HIV RNA <50 copies/ml	85.1% (205)	84.3% (182)	0.8
Current $CD4^+$ cell count (cells/μl)	645 (501; 782)	654 (509; 815)	0.4
Current $CD8^+$ cell count (cells/μl)	714 (533; 922)	698 (531; 941)	0.7
Current $CD4^+/CD8^+$ ratio	0.88 (0.65; 1.17)	0.94 (0.72; 1.26)	0.13
$CD4^+$ cell count >500 cells/μl	75.0% (183)	76.2% (166)	0.8
$CD4^+/CD8^+$ ratio > 1	36.1% (87)	39.8% (84)	0.4

Results are medians (IQR), or % (*n*) of all individuals for whom the datum was available. cART, combination antiretroviral therapy; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI/r, ritonavir-boosted PI.
[a]Last measurement within 6 months prior to the event.
[b]Expressed as years∗$\log_{10}$ HIV-RNA copies/ml.

ratio (as a continuous variable), even after adjusting for total duration of treatment and other known predictive factors (sex, baseline $CD4^+/CD8^+$ ratio, age at cART initiation) (Table 2). We also considered the $CD4^+/CD8^+$ ratio as dichotomized according to 1, and looked for factors associated with achieving a $CD4^+/CD8^+$ ratio more than 1. In both groups, patients with high cumulative HIV viremia (>66th percentile) were less likely than patients with low cumulative HIV viremia (<33rd percentile) to normalize their $CD4^+/CD8^+$ ratio [adjusted odds ratio (OR) 0.34 (0.16–0.75), $P=0.008$, and OR 0.30 (0.13–0.67], $P=0.004$, respectively, after controlling for sex, age, the baseline $CD4^+/CD8^+$ ratio and the total treatment duration. Stratification for number of interruptions (1 vs. >1) in the early treatment group yielded similar results. Other independent predictors of a $CD4^+/CD8^+$ ratio more than 1 were the baseline $CD4^+/CD8^+$ ratio and the cumulative duration of treatment in both groups, and female sex in the deferred treatment group. Overall, 43.3% of patients with low cumulative viremia had achieved a $CD4^+/CD8^+$ more than 1 on cART, vs. 26.6% of patients with high cumulative viremia ($P=0.003$).

Considering cumulative HIV viremia as a function of the restricted cubic spline rather than as a categorized variable yielded similar results. Sensitivity analysis considering a threshold of 50 copies/ml instead of 400 copies/ml also found similar results, although a relationship of borderline significance was found between higher cumulative

Table 2. Impact of cumulative HIV viremia and other factors on the current $CD4^+$ cell count and $CD4^+/CD8^+$ ratio according to the treatment timing: the ANRS PRIMO cohort.

	Difference in mean current $CD4^+$ cell count[a]				Difference in mean current $CD4^+/CD8^+$ ratio[a]			
Factors	Univariate (95% CI)	*P*	Multivariate (95% CI)[b]	*P*	Univariate (95% CI)	*P*	Multivariate (95% CI)[b]	*P*
Early/intermittent treatment								
Cumulative HIV viremia[c]								
<33rd percentile	Ref		Ref		Ref		Ref	
33rd–66th percentile	+11.2 (−67.6 to 89.9)	0.8	−9.3 (−81.8 to 63.3)	0.8	−0.15 (−0.34 to 0.03)	0.11	−0.14 (−0.32 to 0.04)	0.12
>66th percentile	+11.1 (−66.9 to 89.2)	0.8	−63.9 (−141.3 to 13.5)	0.11	−0.29 (−0.47 to −0.10)	0.003	−0.28 (−0.46 to −0.09)	0.003
Women (vs. men)	−20.9 (−104.1 to 62.3)	0.6	−59.7 (−138.3 to 19.0)	0.14	+0.22 (0.02 to 0.42)	0.03	+0.15 (−0.05 to 0.34)	0.14
$CD4^+$ cell count at PHI[d]	+42.9 (29.2 to 56.6)	<0.0001	+49.5 (35.2 to 63.8)	<0.0001				
$CD4^+$/CD8 ratio at PHI[e]					+0.04 (0.02 to 0.06)	<0.0001	+0.05 (0.03 to 0.06)	<0.0001
Age at cART initiation[f]	−11.1 (−43.1 to 20.9)	0.5	−10.9 (−40.2 to 18.4)	0.5	+0.11 (0.03 to 0.18)	0.007	+0.10 (0.03 to 0.17)	0.007
Cumulative treatment duration[g]	+7.8 (−1.7 to 17.3)	0.11	+9.2 (0.3 to 18.1)	0.04	+0.03 (0.004 to 0.05)	0.02	+0.02 (−0.003 to 0.04)	0.09
Deferred/continuous treatment								
Cumulative HIV viremia[c]								
<33rd percentile	Ref		Ref		Ref		Ref	
33rd–66th percentile	−23.7 (−105.9 to 58.4)	0.6	−35.1 (−111.1 to 40.8)	0.4	−0.09 (−0.27 to 0.09)	0.3	−0.07 (−0.22 to 0.09)	0.4
>66th percentile	+18.1 (−62.9 to 99.1)	0.7	−44.8 (−122.4 to 32.9)	0.3	−0.15 (−0.32 to 0.03)	0.11	−0.26 (−0.42 to −0.11)	0.0009
Women (vs. men)	−4.8 (−100.2 to 90.7)	0.9	−3.2 (−91.3 to 84.9)	0.9	+0.51 (0.31 to 0.70)	<0.0001	+0.35 (0.16 to 0.53)	0.0002
$CD4^+$ cell count at PHI[d]	+36.2 (22.4 to 50.0)	<0.0001	+43.3 (29.0 to 57.5)	<0.0001				
$CD4^+/CD8^+$ ratio at PHI[e]					+0.05 (0.04 to 0.07)	<0.0001	+0.05 (0.04 to 0.07)	<0.0001
Age at cART initiation[f]	−37.8 (−69.1 to −6.6)	0.02	−49.9 (−79.2 to −20.5)	0.0009	+0.08 (0.007 to 0.14)	0.03	+0.02 (−0.05 to 0.08)	0.6
Cumulative treatment duration[c]	+11.4 (−6.8 to 29.6)	0.2	+19.2 (2.4 to 36.1)	0.03	+0.03 (−0.009 to 0.07)	0.13	+0.04 (0.007 to 0.08)	0.02

CI, confidence interval.
[a]From linear regression model; the model provides the difference in means $CD4^+$ cell count or means $CD4^+/CD8^+$ ratio between the modalities of a variable, one modality being the reference.
[b]Adjusted for all variables listed in the column.
[c]Cumulative HIV viremia in the early/intermittent treatment group: 33rd percentile = 6.96; 66th percentile = 13.14; in the deferred/continuous treatment group: 33rd percentile = 7.42; 66th percentile = 12.72.
[d]Per 100 cells/μl higher.
[e]Per 0.1 increase.
[f]Per 10-year increase.
[g]Per 1-year increase.

viremia (>66th percentile vs. <33th percentile) and lower current $CD4^+$ cell count (adjusted mean difference of $CD4^+$ cell count −72.7 cells/μl, $P = 0.06$), only in the early/intermittent group.

Influence of the timing of combination antiretroviral therapy initiation on current immunological status

The role of the timing of cART initiation was studied. Overall, or when restricted to patients on suppressive cART (current viral load <50 copies/ml) (Table 3), we found no difference in the current $CD4^+$ cell count between early and deferred treatment [crude mean difference in $CD4^+$ cell count −4.8 cells/μl (95% confidence interval, 95% CI: −61.5 to 51.8), $P = 0.9$], even after controlling for sex, age, the $CD4^+$ cell count at PHI diagnosis and the cumulative duration of treatment. This result was not affected by further adjustment for cumulative HIV viremia [+5.3 (95% CI: −51.0 to 61.7), $P = 0.8$].

Conversely, the group of patients treated continuously since PHI (i.e. with very low exposure to cumulative viremia) had a significantly higher current $CD4^+$ cell count (mean difference: >100 cells/μl $CD4^+$ cell count) and $CD4^+/CD8^+$ ratio (mean difference: >0.26), than the early/intermittent and deferred treated patients (Table 3). They reached a median of 731 cells/μl $CD4^+$ cell count after a median of 2.5 years of continuous treatment; the $CD4^+/CD8^+$ ratio was more than 1 in 64.1% of patients.

Discussion

This is the first study to examine, in patients followed since primary HIV infection, the impact of cumulative HIV viremia since HIV infection on current immunological status, according to the timing of cART initiation. In neither the early/intermittent nor the deferred/continuous treatment group was cumulative HIV viremia a significant predictor of the $CD4^+$ cell count reached after long-term treatment. In contrast, cumulative HIV viremia was an independent predictor of the current $CD4^+/CD8^+$ ratio in both groups.

One of the major strengths of our study is the long duration of patient follow-up, which started during PHI (median of 9 years for patients who received early/intermittent treatment and 6 years for patients who received deferred/continuous treatment), allowing us to analyse the impact of long-term exposure to HIV replication. One limitation is that viremic episodes occurring during short treatment interruptions might have been missed.

Consistently with previous studies [22–25], we found that the $CD4^+$ cell count reached after long-term treatment was significantly associated with the total duration of treatment. As stated by Kulkarni *et al.* [28], we also found a significant association with the $CD4^+$ cell count at PHI diagnosis, which is slightly different from the pretherapy $CD4^+$ cell count, which has been extensively reported as a strong independent predictor [26–32]. The $CD4^+$ cell count reached after long-term treatment was not associated with exposure to viremia more than 400 copies/ml cumulated since PHI, whether before starting deferred treatment or during interruptions of treatment started during PHI. This suggests that $CD4^+$ cell recovery after several years of treatment is driven less by lifelong viremia than by the degree of $CD4^+$ cell count depletion before starting ART, which may be influenced by genetic and/or immunologic factors.

We had hypothetized that prolonged exposure to HIV replication and the resulting immunological damage incurred when treatment is deferred would have a more detrimental impact than one or more viremic episodes during interruptions of early treatment. Indeed, a recent study of protocol-indicated ART discontinuation showed that the viremic rebound after discontinuing ART initiated during PHI was smaller than that observed after discontinuing ART initiated during the chronic phase of infection [12]. However, this study did not investigate further impact on $CD4^+$ cell counts, $CD4^+/CD8^+$ ratio or clinical outcome after treatment resumption. In our study, exposure to prolonged HIV replication before ART initiation did not have a worse impact than one or more episodes of viremia during interruption(s) of early treatment in terms of $CD4^+$ cell count recovery. Indeed, we even found that cumulated exposure to viremia more than 50 copies/ml tended to be more deleterious for current $CD4^+$ cell count in early/intermittent treatment than in deferred/continuous treatment, but the relationship was of borderline significance.

It is noteworthy that most of the patients who started treatment during PHI were virologically suppressed and had $CD4^+$ cell counts above 500 cells/μl on current treatment resumption, despite one or several previous treatment interruptions. Nevertheless, despite a high percentage of time spent on treatment (75%) and a long duration of current treatment (almost a median of 5 years), only 36% of patients had attained a $CD4^+/CD8^+$ ratio more than 1. This contrasts with reported results for patients receiving continuous treatment since primary infection, in whom the median $CD4^+/CD8^+$ ratio raised up to above 1, here and in other studies [7,33]. A deleterious effect of serial interruptions of treatment initiated during PHI was also observed in the ANRS Interprim trial, in which a gradual decline in the $CD4^+/CD8^+$ ratio was observed after repeated short interruptions [7]. We found that lifelong cumulative HIV viremia significantly influenced the current $CD4^+/CD8^+$ ratio in

Table 3. Impact of timing of combination antiretroviral therapy initiation on current $CD4^+$ cell count and current $CD4^+/CD8^+$ ratio: the ANRS PRIMO cohort.

	Difference in mean current $CD4^+$ cell count				Difference in mean current $CD4^+/CD8^+$ ratio			
Factors	Univariate (95% CI)	*P*	Multivariate (95% CI)[a]	*P*	Univariate (95% CI)	*P*	Multivariate (95% CI)[a]	*P*
Treatment group								
Deferred/continuous tt	Ref		Ref		Ref		Ref	
Early/intermittent tt	−4.8 (− 61.5 to 51.8)	0.9	+17.9 (− 40.9 to 76.7)	0.6	−0.02 (−0.14 to 0.09)	0.7	+0.01 (−0.11 to 0.14)	0.8
Early/continuous tt	+65.9 (10.5 to 121.2)	0.02	+124.9 (71.9 to 177.9)	<0.0001	+0.18 (0.06 to 0.29)	0.002	+0.27 (0.16 to 0.37)	<0.0001
Women (vs. men)			−13.2 (−71.8 to 45.5)	0.7			+0.23 (0.11 to 0.35)	0.0003
$CD4^+$ cell count at PHI[b]			+48.5 (39.2 to 57.8)	<0.0001				
$CD4^+/CD8^+$ at PHI[c]							+0.05 (0.04 to 0.06)	<0.0001
Age at cART[d]			− 23.1 (− 42.8 to − 3.3)	0.02			+0.05 (0.02 to 0.09)	0.01
Cumulative treatment duration[e]			+8.0 (1.3 to 14.7)	0.02			+0.01 (−0.001 to 0.03)	0.07

cART, combination antiretroviral therapy; CI, confidence interval.
[a]Adjusted for all variables listed in the column.
[b]Per 100 cells/μl higher.
[c]Per 0.1 increase.
[d]Per 10-year older.
[e]per 1 year increase.

both the early/intermittent and deferred/continuous treatment groups, even after adjusting for the cumulative duration of treatment and the $CD4^+/CD8^+$ ratio at PHI diagnosis. This probably explains the discrepancy between the good long-term $CD4^+$ cell count recovery and the far poorer $CD4^+/CD8^+$ recovery. This is a major result, as low $CD4^+/CD8^+$ ratios on cART are associated with inflammation/immune activation [34] and increased morbidity/mortality [19,20].

During the chronic phase of infection, it has been reported that immune reconstitution is generally poorer after treatment resumption than during first-line ART [35–37]. Here, we found that among patients with current viral suppression on cART, the current $CD4^+$ cell count was similar in the early/intermittent and deferred/continuous treatment groups. However, this must not be interpreted as if interruptions of early treatment were not deleterious. Indeed, such interruptions are deleterious: 12 cases of AIDS-defining events occurred, most of them could have been probably avoided without these interruptions and the percentage of patients who reached a $CD4^+/CD8^+$ ratio greater than 1 was low. In contrast, patients treated continuously since PHI exhibited much higher $CD4^+$ cell count and $CD4^+/CD8^+$ ratio. No AIDS-event occurred during the follow-up in this group.

It is noteworthy that current $CD4^+$ cell count was not higher in the early/intermittent treatment than in the deferred/continuous group, given the longer duration of the current continuous treatment (4.8 compared with 3 years). This would support the hypothesis that cumulated exposure to viremia is more deleterious for $CD4^+$ cell count recovery in early/intermittent treatment than in deferred/continuous treatment, although the negative association found between cumulative HIV viremia and current $CD4^+$ cell count in the early/intermittent treatment group was of borderline significance. However, as in any observational study, there could be some confounding factors that could not be taken into account. We cannot exclude that the early treated patients were individuals with worse prognosis than those for whom the decision was to differ treatment initiation, although we tried to consider this by adjusting for baseline $CD4^+$ cell count or baseline $CD4^+/CD8^+$ ratio.

HIV treatment guidelines have evolved during the last decade. Treatment interruption after early initiation of cART during primary infection has no longer been recommended. The $CD4^+$ cell count threshold at which treatment initiation is recommended has gradually increased and the latest French guideline (2013) recommends treatment initiation for all patients at diagnosis, regardless of their $CD4^+$ cell count. This has resulted in a higher proportion of patients being treated early after infection. Even if recent drugs are better tolerated, unscheduled treatment interruptions continue to occur, mainly because of suboptimal adherence or

irregular follow-up. Our results underline the need to reinforce patient support during early treatment in order to maintain adherence to what is still a lifelong treatment.

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Appendix

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