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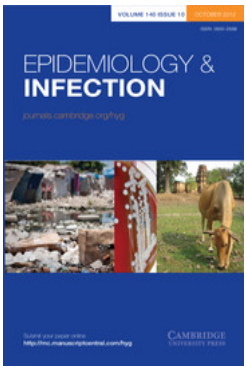

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The rate of CD4 decline as a determinant of progression to AIDS independent of the most recent CD4 count

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SUMMARY

The data of two cohort studies of HIV-infected individuals were used to examine whether the rate of CD4 decline is a determinant of HIV progression, independent of the most recent CD4 count. Time from seroconversion to clinical AIDS was the main outcome measure. Rates of CD4 decline were estimated using the ordinary least squares regression method. AIDS incidences were compared in individuals who had previously experienced either a steeper or a less steep rate of CD4 decline. Cox proportional hazards model including a time-dependent covariate for the rate of CD4 decline was performed. The rate of prior CD4 decline was significantly associated with the risk of developing AIDS independently from the most recent CD4 count, with a 2% increase in hazard of AIDS ($P < 0{\cdot}01$) for a difference of 10 cells/mm^3 in the estimated yearly drop in CD4 count. This finding gives scientific credit to the belief that individuals with a prior steeper CD4 decline consistently have a higher subsequent risk of developing AIDS than those with a less steep prior decline.

INTRODUCTION

Despite reports that plasma viral load strongly predicts progression to AIDS and death, the CD4 lymphocyte count remains an important marker for short term predictions of the risk of AIDS of death in HIV-infected individuals [1–5]. Previous studies have shown that if the CD4 count is known, the time from seroconversion seems to be of little additional value when assessing the risk of progression to AIDS [6, 7]. A recent report from the Multicenter AIDS Cohort Study (MACS) confirmed these results using regression modelling [8]. These findings would suggest that prior rate of CD4 decline may not add much prognostic information if the current CD4 count is known. However, whilst time from seroconversion certainly correlates with the rate of CD4 decline, it only provides information as to the probable history of CD4 decay. Models which incorporate accurate estimates of such a decline are needed to answer to the question: 'given a certain level of CD4 count, is there a differential risk of developing AIDS according to individuals' previous pattern of CD4 decline ?' and if so to quantify this effect. Some authors either assumed

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or showed that the most recent CD4 count is sufficient for predicting a diagnosis of AIDS [9–11]. In contrast, it has been suggested that the underlying pattern of CD4 decline may provide a more powerful indicator for HIV disease progression than the CD4 count itself [12–15]. Saah and colleagues [13] found that the decline in the CD4 count during the first 6 months of follow-up was associated with the risk of developing AIDS independently from the CD4 percentage and recently Chêne and colleagues [14] showed that among patients whose CD4 count reached 50 cells/mm^3 a steeper prior rate of CD4 decline was associated with a poorer survival independently from the actual CD4 count. In contrast, Yong and colleagues [15] reported that individuals who have a low CD4 count for a period of 6 months have higher immediate risk of AIDS than individuals who have just decreased to that level from a higher level 6 months earlier.

In this study we used the data of the Italian Seroconversion Study Cohort (ISSC) and those of the Royal Free Hospital Haemophilia Cohort (RFHHC) of HIV-infected haemophilic individuals to determine whether the rate of CD4 decline is a determinant of HIV progression, independent of the most recent CD4 count. The use of both cohorts allowed the issue to be addressed in individuals who became infected through all the main modes of HIV transmission; i.e. injecting drug use, sexual contacts and receipt of contaminated blood products.

METHODS

Details of the ISSC and RFHHC have been fully described elsewhere [16, 17]. In brief, the ISSC includes 1292 HIV-infected individuals with a documented negative test for HIV followed by a confirmed positive test within 2 years. It is an ongoing study in 16 centres and includes individuals who acquired HIV by sharing needles or through sexual contact. The RFHHC consists of 111 men with haemophilia infected with HIV during 1979–85 after treatment with contaminated blood products. Retrospective testing of stored serum samples and the introduction of sterilized blood products in 1985, have enabled the seroconversion dates to be estimated with a maximum error of 2 years for 83 (74·8%) of individuals.

In addition to demographic information such as gender and age, full clinical examinations and measures of CD4 lymphocyte count were conducted about every 6 months in both cohorts; regular monitoring of CD4 count started in 1982. CD4 subset studies were performed by flow-cytometry, using standardized techniques (Ortho diagnostics, Raritan, New Jersey, USA and Becton Dickinson, Crowley, UK for ISSC and RFHHC respectively).

The Italian AIDS surveillance registry and census bureau were used to minimize loss to follow up and to check vital status of individuals enrolled in the ISSC whose last clinical visit was at least 2 years before 31 July 1995. Clinical Status was known on all members of the RFHHC up to 1 January 1996.

Study population

Nine hundred and eighty-three individuals of the ISSC and 103 of the RFHHC with at least three CD4 measurements, for whom we could accurately estimate the rate of CD4 decline, were included in the analysis.

Statistical analysis

A clinical diagnosis of AIDS according to the European Center for Diseases Control definition in use at the time of the event occurring [17, 18] was the main endpoint of the analysis. To evaluate the influence of the rate of CD4 decline on the course of HIV progression, incidence rates of developing AIDS (per 1000 person-years) after an individual had reached a certain pre-defined CD4 level (300, 200 and 100 cells/mm^3) were calculated. Incidence rates were compared in individuals who had a 'steeper' or 'less steep' estimated rate of CD4 decline prior to their CD4 count falling below the cut-off level. The time point t at which an individual was estimated to decline below a given CD4 count level was determined by linear interpolation between the first count below that level and the previous count. In defining the rate of CD4 count decline prior to the date of reaching this cut-off, we considered the ordinary least square estimates of the slopes calculated over the previous 5 years before t. Individuals were divided into 'slow decline' or 'fast decline' if their estimated slope was below (less steep) or above (steeper) the median population slope. This was possible only for patients with at least two CD4 counts over the previous 5 years before t.

For the ISSC data, AIDS-free time was calculated as the time from seroconversion to AIDS diagnosis for those who developed AIDS and the time from seroconversion to 31 July 1995 for those without an AIDS diagnosis. AIDS-free time for individuals in the RFHHC was calculated as the time from seroconversion to AIDS diagnosis or 31 December 1995 whichever happened first. Follow-up times of individuals who died before developing AIDS were

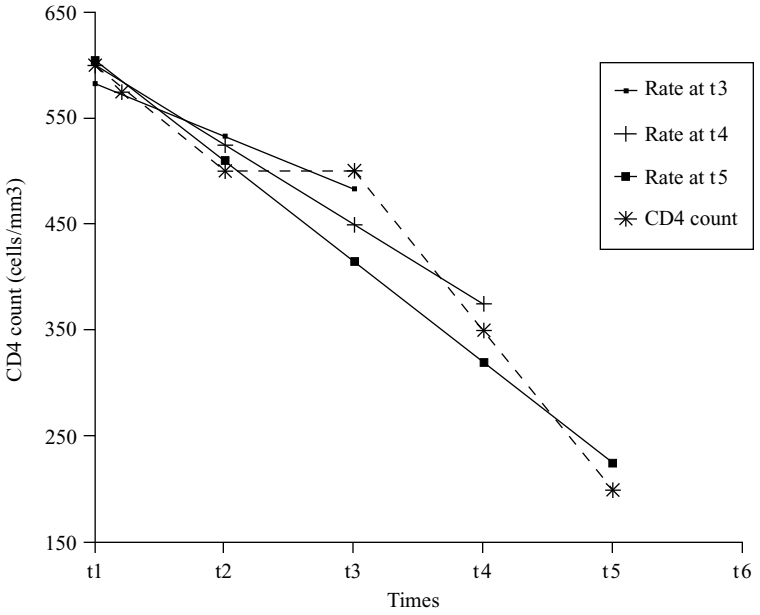

Fig. 1. Calculation of a time-dependent estimate for the rate of CD4 count decline in one individual. The slope coefficient of the regression line fitted using CD4 counts measured up to time t_j ($j = 3, 4, 5$) gives the estimate of the rate of CD4 count decline at time t_j.

censored at the date of death. A standard Cox proportional hazards model was used for the multivariate analysis. The model included time-dependent covariates for the most recent CD4 count, the previous rate of CD4 count decline and the antiretroviral treatment usage. The covariate expressing the treatment usage was a time dependent indicator taking the value zero until the point in time when the individual first received antiretroviral treatment and 1 thereafter. Treatment was included in the model on an 'intention to treat' basis (i.e. the covariate remained set to one irrespective of whether the patient stopped treatment). This was done because antiretroviral therapy has been shown to affect the CD4 count and to delay the onset of AIDS [18–21]. Antiretroviral treatment included treatment with zidovudine (ZDV), didanosine (ddI) or zalcitabine (ddC) (mainly monotherapy). Age at seroconversion was also included since its association with progression to AIDS is well established [22, 23]. In the Cox regression the previous rate of CD4 decline was estimated by least squares regression for each individual using the CD4 counts measured up to the most recent time point (see below).

A time dependent covariate for the estimated rate of CD4 decline

A new CD4 count had the effect of changing both the most recent value for the CD4 count and the estimate of the rate of decline in the model. Thus, for example, if an individual had 600, 500, 500, 350 and 200 cells/mm^3 at yearly-spaced times t_1–t_5, respectively, the covariate containing the value for the slope would be missing at times t_1 and t_2 (three measurements was the required condition for a sufficiently accurate estimate), -50 at time t_3, -75 at time t_4, and -95 at time t_5 (Fig. 1). Initially the slopes were estimated using all the CD4 counts collected since the estimated date of seroconversion. As a further analysis only those collected over the last 5 years (for those with at least 2 CD4 count over the last 5 years of follow-up) were included in the slope calculations. To test the hypothesis of a differential effect of the rate of CD4 decline according to the level of CD4 count (interaction between the rate of decline and the most recent CD4 count), variables containing the estimated rate of CD4 decline when the CD4 count was included in pre-defined bands (e.g. < 100, 100–300 and 300–500 cells/mm^3) were added to the model. Similar results were found whichever pre-defined bands were chosen. For convenience, all the analyses were performed using the untransformed scale for the CD4 count, the conclusions being similar when the logarithmic scale for the CD4 count or the square root scale for calculating the slopes of CD4 count decline were used. All statistical analyses were carried out using Statistical Analysis Software (SAS) [24].

RESULTS

A description of the study populations according to gender, mode of transmission, antiretroviral treatment

Table 1. *Description of the ISSC and RFHHC study populations**

	ISSC		RFHHC	
	Number	Per cent	Number	Per cent
Gender				
Male	693	70·5	103	100·0
Female	290	29·5	—	—
Mode of transmission				
Injecting drug use	498	50·7	—	—
Homosexual contacts	281	28·6	—	—
Heterosexual contacts	187	19·0	—	—
Blood products recipient	—	—	103	100·0
Other	17	1·7	—	—
Antiretroviral treatment†				
Yes	495	50·4	59	57·3
No	488	49·6	51	42·7
AIDS				
Yes	213	21·7	49	47·6
No	770	78·3	58	52·4
	Median (range)		Median (range)	
Age at seroconversion (years)	27 (14–66)		21 (2–62)	
Follow-up time‡ (years)	5·21 (0·87–14·37)		12·77 (3·01–16·18)	
Number of CD4 count measurements	7 (3–28)		26 (3–75)	

* Only individuals with at least 3 measurements of CD4 count.
† ZDV, ddI, ddC (mainly monotherapy).
‡ Calculated as the time to death for the individuals who died or the time to the date of cut-off of the study for those still alive.

Table 2. *Risk of AIDS* (*calculated as rates per 1000 person years*) *according to the level of CD4 count in individuals who experienced either a steeper or less steep rate of CD4 count decline* (*estimated using ordinary least squares method*) *over the 5 years prior to the CD4 count falling below the cut-off level*

	ISSC			RFHHC		
	Current CD4 count (cells/mm^3)			Current CD4 count (cells/mm^3)		
	300	200	100	300	200	100
Median prior drop (cells/mm^3 per year)	79	93	94	70	63	72
Rate of CD4 decline < median (less steep)						
Number	191	156	97	26	32	22
AIDS	10	25	41	12	18	11
Person-years (pyrs)	4722·5	2958·8	1015·3	1134·4	964·9	418·7
Rate (per 1000 pyrs)	2·12	8·45	40·38	10·58	18·65	26·27
⩾ median (steeper)						
Number	191	157	98	26	32	22
AIDS	19	35	45	14	21	18
Person-years (pyrs)	4865·1	2820·1	886·6	1183·4	1029·2	440·5
Rate (per 1000 pyrs)	3·91	12·41	50·76	11·83	20·41	40·86
Total						
Number	382	313	195	52	64	44
Relative rate	1·84	1·47	1·26	1·12	1·09	1·56
(95% CI)	(0·82–4·44)	(0·85–2·56)	(0·81–1·97)	(0·48–2·65)	(0·55–2·18)	(0·70–3·65)

Table 3. *Relative hazards of developing AIDS from fitting a Cox model with a time dependent covariate for the estimated slopes in the ISSC*

	Relative hazards of AIDS (95% CI)	
Covariates	Crude	Adjusted*
All CD4 counts since the date of SC		
Most recent CD4 count	1·830 (1·682–1·992)	1·783 (1·600–1·986)
(per 100 cells/mm^3 lower)	$P = 0{\cdot}0001$	$P = 0{\cdot}0001$
Rate of CD decline	1·028 (1·019–1·036)	1·022 (1·009–1·035)
(per 10 cells/mm^3 difference in yearly drop)	$P = 0{\cdot}0001$	$P = 0{\cdot}0006$
CD4 counts over the previous 5 years		
Most recent CD4 count	1·830 (1·682–1·992)	1·779 (1·597–1·981)
(per 100 cells/mm^3 lower)	$P = 0{\cdot}0001$	$P = 0{\cdot}0001$
Rate of CD4 decline	1·028 (1·020–1·037)	1·024 (1·011–1·036)
(per 10 cells/mm^3 difference in yearly drop)	$P = 0{\cdot}0001$	$P = 0{\cdot}0002$

* Adjusted estimates refer to the model comprising the most recent CD4 count, the ordinary least squares estimates of the slope of CD4 decline, age and treatment usage.

usage and AIDS cases is given in Table 1. The median and range of age at seroconversion, length of follow up, and number of CD4 count measurements are also reported. All patients in the RFHHC seroconverted during 1979–85. As a result, patients in this cohort had a longer follow-up and more CD4 measurements, on average, than those in the ISSC which includes seroconversions up to July 1995. A higher proportion of AIDS cases was also observed in the RFHHC as a result.

Table 2 shows the risk of AIDS, calculated as rates per 1000 person-years (pyrs), conditioning on the level of current CD4 count in individuals who experienced either a less steep or a steeper rate of CD4 decline over the previous 5 years. It is clear from this table that the risk of AIDS strongly increases as individuals reach lower levels of the current CD4 count; the risk of AIDS for a current count of 100 cells/mm^3 was 3–4 times bigger than that at 300 cells/mm^3 in the RFHHC and 13–20 times in the ISSC. Individuals who experienced a faster decline in CD4 count over the previous 5 years were at higher risk of developing AIDS than those with slower prior declines at each CD4 level (300, 200 or 100 cells/mm^3). Although the association was not significant at the conventional level of 0·05, this crude analysis performed using the data from ISSC and from the RFHHC consistently showed rate ratios above one when comparing the 2 groups of individuals (Table 2). So, for example, the risk of developing AIDS for an individual in the RFHHC with a current CD4 count of 300 cells/mm^3 and having a rate of CD4 decline of 70 cells per year or more is 12% higher than that of someone with the same level of CD4 count but a less rapid rate of CD4 decline (< 70 cells per year). Very similar results were obtained when the slopes were calculated using the CD4 counts observed only over the 3 years before the pre-defined cut-off, which was considered as the shortest period required to obtain an accurate estimate using the least squares method (data not shown).

Results from fitting the Cox model confirmed those of the crude analysis (Tables 3, 4). The effect of the most recent CD4 count was still the most important factor in predicting an AIDS event after adjusting for the estimated rate of CD4 decline and the other covariates considered (Wald $\chi^2 = 110{\cdot}3$, $P = 0{\cdot}0001$ and Wald $\chi^2 = 33{\cdot}8$, $P = 0{\cdot}0001$, in the ISSC and RFHHC respectively). Whilst the effect of the estimated rate of CD4 decline was reduced after adjusting for the most recent CD4 count it remained associated with the outcome independently of the most recent count, age at seroconversion and treatment usage (Wald $\chi^2 = 11{\cdot}6$, $P = 0{\cdot}0006$ and Wald $\chi^2 = 5{\cdot}8$, $P = 0{\cdot}02$, in the ISSC and RFHHC respectively). From the estimated coefficients a difference of 10 cells/mm^3 in the estimated yearly drop in CD4 count was associated with about 2% increase in risk of AIDS, the individuals with a faster decline being at higher risk. The effect was slightly bigger and marginally more significant when the estimates of the slope were calculated considering the CD4 counts observed only over the last 5 years (Tables 3, 4). As with the crude analysis, virtually identical results were found when considering CD4 counts observed only over the last 3 years (data not shown). To test the hypothesis of a different predictive value of the rate of CD4 decline according to the most recent CD4 count, an interaction term between these 2 variables has been

Table 4. *Relative hazards of developing AIDS from fitting a Cox model with a time dependent covariate for the estimated slopes in the RFHHC*

	Relative hazards of AIDS (95% CI)	
Covariates	Crude	Adjusted*
All CD4 counts since the date of SC		
Most recent CD4 count	1·766 (1·492–2·090)	1·809 (1·481–2·210)
(per 100 cells/mm^3 lower)	$P = 0{\cdot}0001$	$P = 0{\cdot}0001$
Rate of CD decline	1·024 (1·004–1·045)	1·017 (1·003–1·031)
(per 10 cells/mm^3 difference in yearly drop)	$P = 0{\cdot}02$	$P = 0{\cdot}02$
CD4 counts over the previous 5 years		
Most recent CD4 count	1·766 (1·492–2·090)	1·802 (1·476–2·199)
(per 100 cells/mm^3 lower)	$P = 0{\cdot}0001$	$P = 0{\cdot}0001$
Rate of CD4 decline	1·026 (1·005–1·048)	1·018 (1·004–1·033)
(per 10 cells/mm^3 difference in yearly drop)	$P = 0{\cdot}01$	$P = 0{\cdot}01$

* Adjusted estimates refer to the model comprising the most recent CD4 count, the ordinary least squares estimates of the slope of CD4 decline, age and treatment usage.

added to the initial model. Since there was no statistical evidence for an interaction and the relative hazards calculated at various levels of the most recent CD4 count were very similar, the covariate expressing the interaction effect was excluded from the final model.

DISCUSSION

The results of this study clearly show that the entire history of CD4 count contains additional prognostic information to the most recent CD4 count. In particular, individuals whose CD4 counts have fallen most rapidly are those with the highest risk of AIDS even when the current CD4 count is controlled for. Some evidence of the existence of this effect was found when comparing the rates of developing AIDS after an individual had reached a certain pre-defined CD4 level in 2 groups of individuals whose prior rate of CD4 decline was steeper or less steep than the population average. Whilst this was a very crude analysis, mainly for illustrative purposes, a more powerful analysis, involving the use of the Cox proportional hazards model with an updated covariate containing the continually changing estimate of the rate of CD4 decline, adjusted for the continually changing most recent CD4 count, showed that the significance of the association is much higher ($P < 0{\cdot}01$). These results are drawn from two different cohorts of individuals for whom an accurate estimate of the date of seroconversion is available. Hence, it is unlikely that our findings are simply a consequence of biases in the estimates of AIDS-free time. All the main modes of HIV transmission (i.e. injecting drug use, sexual contacts and receipt of contaminated blood products) were represented across the 2 cohorts so our results apply to all individuals irrespective of how they acquired HIV infection. Further, results were virtually identical when the analyses were repeated considering death as the endpoint (data not shown).

Our findings although consistent with those found by previous studies [13–15] are in contrast with those reported elsewhere [10, 11] that the current CD4 count alone is sufficient to predict future progression. However, this discrepancy might be explained by the different statistical methods used. Our results also contradict one of the assumptions of the continuous-time Markov model [12]. However, the magnitude of the effect, after adjusting for the most recent CD4 count, is small (2% increase in risk per 100 cells/mm^3 difference in yearly drop in CD4 count) compared to the risk for 100 cells/mm^3 difference in the CD4 count (about 80% increase). Therefore, it is unlikely that failing to incorporate this effect in Markov models would have a major effect on results.

Previous studies using data from these 2 cohorts [7, 8] and the data of the MACS [9], suggested that the prior history of CD4 decline in a given patient could be ignored when assessing the risk of AIDS once his/her most recent CD4 count is known. These studies did not, however, consider an accurate estimate of the CD4 count decline explicitly in the analyses and, as a result, these finding are not directly comparable. For example, it is possible that 2 individuals may have the same current level of CD4

count at different times after seroconversion simply because their CD4 count at seroconversion was different while they may well have experienced the same mean CD4 decline.

The possible biases and limitations of this study should be mentioned before drawing firm conclusions. First of all, given the lack of plasma viral load data in these cohorts we cannot rule out the possibility that the rate of CD4 decline is a simple surrogate of individuals' levels of viraemia i.e. that individuals with the steepest CD4 decline are also those with the highest plasma viral load. It remains to be seen if the prognostic role of the rate of CD4 decline is confirmed once measurements of plasma viral load are available for these patients.

The results obtained using the Italian cohort might be biased by the exclusion of 309 individuals of the ISSC, 24% of the entire cohort, who had fewer than three CD4 count measurements. These individuals are more likely to be the faster progressors or recent seroconverters; almost a half of these patients seroconverted after 1990. Unfortunately, we did not have enough CD4 measurements to calculate an accurate estimate of their rate of CD4 decline, so we could not assess the prognostic value of the rate of CD4 decline in this subgroup of individuals. However, median age and baseline CD4 count were similar in the group of patients excluded and in those used for this analysis; median age was 26 (range 17–59) in patients excluded compared to 27 (range 14–66, Table 1) in the study population and the median baseline CD4 count was 594 (range 5–1875) and 629 (range 5–1984), respectively.

The usage of nucleoside monotherapy has been shown to delay progression to AIDS and to have a small impact on the CD4 count [18–21]. Since the CD4 count is not a perfect surrogate for the development of AIDS, the association between the rate of CD4 decline and the risk of AIDS in the individuals who received treatment might simply be a result of bias. However, the effect of prior CD4 decline remains significant after adjusting for treatment usage. More recently, the introduction of protease inhibitors and treatment strategies which include these potent drugs in combination with nucleosides, appears to have led to reductions in the risk of AIDS and dramatic changes in CD4 counts following treatment [27–29]. As these patients were followed up until the end of 1995, no patients had the opportunity to receive these potent drug regimens. However, it is unclear what the effects of these treatment-induced changes will have on the result of our study and we await the opportunity to study this issue at a later date when sufficient data is available for the analysis.

While it is well established that in treatment-naïve or lightly treated patients the general underlying CD4 trend is one of monotone decay, there is no agreement on the best explanatory model for estimating individual and population rates of CD4 count decline. The most common assumption is that the underlying pattern of CD4 decline is linear on the square root scale [10, 27–30]. Even if the linear assumption (on the raw CD4 count) may not be the 'correct' model to explain the biologic complexity of the rate of CD4 decline, in this paper we used this assumption because we believed that it was sufficiently successful to obtain good 'working' estimates of the rate of CD4 decline over the relatively short term and that the actual number of CD4 cells is more familiar to clinicians than any other transformed figure. Further, we drew the same conclusions when we repeated the analysis using the logarithmic or the square root transformation of CD4 count both for the most recent count and for estimating the rate of decline.

When searching for pathogenic mechanisms the relationship between the true underlying CD4 count and the disease progression is of primary interest. However, despite the introduction of new laboratory methods and quality control schemes to standardize methods, the CD4 count remains an imperfectly measured marker and the observed relationship between the measured CD4 count and HIV progression may not be the same as the relationship between the underlying CD4 trend and the disease.

In conclusion, these data provide evidence that the rate of CD4 decline provides additional prognostic information which is not contained in the most recent CD4 count. Whilst the effects reported are relatively small and, as such, are unlikely to dramatically alter clinical decisions, our study recognised the predicting role of the rate of CD4 decline, a refining step in the process of defining markers of HIV progression.

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