Prevalence and comparative characteristics of long-term nonprogressors and HIV controller patients in the French Hospital Database on HIV

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Objective: To estimate the prevalence and characteristics of long-term nonprogressor (LTNP) and HIV controller patients in a very large French cohort of HIV1-infected patients.

Methods: In the French Hospital Database on HIV [FHDH, Agence Nationale de Recherches sur le SIDA et les hépatites virales (ANRS) CO4], we selected patients who had been seen in 2005, who had been infected for more than 8 years, who were treatment-naive, and who remained asymptomatic. Patients with these characteristics then categorized as follows: LTNP ($\geq$8 years of HIV infection and CD4 cell nadir $\geq$500/μl), elite LTNP ($\geq$8 years of HIV infection, CD4 cell nadir $\geq$600/μl, and a positive CD4 slope), HIV controllers (>10 years of HIV infection with 90% of plasma viral load values $\leq$500 copies/ml), and elite controllers (same as HIV controllers, but with last plasma viral load value $\leq$50 copies/ml in 2005).

Results: Among the 46 880 HIV1-infected patients followed in 2005 in the French Hospital Database on HIV, 0.4% ($N=202$) were LTNP, 0.05% ($N=25$) were elite LTNP, 0.22% ($N=101$) were HIV controllers, and 0.15% ($N=69$) were elite controllers. Ten elite LTNP patients (40%) were also HIV controllers, eight (32%) were elite controllers, and 60% had detectable plasma viral load (>50 copies/ml). Among the elite controllers, 32 (46%) were LTNP, eight (12%) were elite LTNP, and one-quarter had a last CD4 cell count less than 500/μl.

Conclusion: LTNP, elite LTNP, HIV controller, and elite controller patients are rare phenotypes. Elite LTNP patients are less frequent than HIV controllers. There is little overlap among the four subgroups of patients.

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Keywords: elite controller, HIV controller, HIV/AIDS, long-term nonprogressor

Introduction

Some HIV1-infected patients, known as long-term nonprogressors (LTNP), remain asymptomatic for many years and maintain high CD4 cell counts without antiretroviral therapy. After the introduction of routine HIV RNA assays during patient follow-up, new groups of patients with slow disease progression were defined by virologic parameters and no more by immunologic parameters; these patients who spontaneously control viral replication are called 'HIV controllers' and a subset are known as 'elite controllers'.

The definitions of these patient groups vary in the literature [1–5], because of differences in available biomarkers (CD4 and/or HIV RNA), the choice of

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different cutoffs (≥500 or ≥600 CD4 cells/μl, ≤50 or ≤500 copies of HIV RNA/ml), and different lengths of follow-up. Initial studies used a treatment-free survival time of 6–8 years, whereas subsequent studies used periods of more than 10 years, which also corresponded to the median AIDS incubation period before the introduction of combination antiretroviral treatment (cART).

Regardless of precisely how they are defined, these patient groups represent useful models of natural protection against disease progression, and the underlying mechanisms may have important implications for prophylactic and therapeutic vaccine research.

Here we examined the respective prevalence and characteristics of LTNP and HIV controller patients enrolled in a large prospective cohort of HIV-infected patients. A secondary objective was to examine to what extent the definitions of these patient groups overlap.

Patients and methods

Patients

We selected all asymptomatic, antiretroviral-naïve patients over 13 years of age who were known to have been infected by HIV for at least 8 years, who attended a FHDH follow-up visit in 2005, and for whom at least three CD4 cell and HIV RNA values were available during the previous 5 years. The French Hospital Database on HIV [FHDH, Agence Nationale de Recherches sur le SIDA et les hépatites virales (ANRS) CO4] is a nationwide hospital-based cohort created in 1989, in which clinical and biological data on HIV-infected patients throughout France are prospectively recorded. Since late 2005, 114 199 HIV1-infected patients have been enrolled in FHDH, and 46 880 patients seen in 2005 had both available CD4 cell and HIV RNA values and known dates of HIV infection.

Methods

We studied the selectivity of the different definitions of LTNP patients and of HIV controllers.

LTNP patients are generally defined on the basis of the CD4 cell count nadir (≥500 /μl or ≥600/μl) and on CD4 cell count stability over time. For this study, we considered that a positive CD4 cell count regression slope over the 5 years prior to 2005 indicated CD4 cell count stability over time.

HIV controllers were defined as patients in whom 90% of plasma HIV RNA values during follow-up were 500 copies/ml or less, and we further distinguished patients whose last plasma HIV RNA value in 2005 was below 50 copies/ml.

We then chose to specifically describe four groups of patients defined elsewhere, namely, patients with at least 8 years of HIV infection and a CD4 cell count nadir of at least 500/μl [6], referred to as 'LTNP'; 'elite LTNP patients' with at least 8 years of HIV infection, a CD4 cell count nadir of at least 600/μl, and a positive CD4 cell slope [7]; 'HIV controllers' with more than 10 years of HIV infection and 90% of plasma HIV RNA measurements of 500 copies/ml or less [3]; and 'elite HIV controllers' infected for more than 10 years with 90% of plasma HIV RNA measurements of 500 copies/ml or less and a last HIV RNA value below 50 copies/ml [8,9].

Results

Among the 46 880 HIV1-infected patients followed in the FHDH in 2005, 28 135 (60%) had been infected more than 8 years previously (Fig. 1). Of these, 27 257 patients (96.9%) had at least three available plasma HIV RNA and CD4 cell values obtained during the previous 5 years. Of these, 19 390 patients (71.1%) were asymptomatic and 903 patients (4.7%) were antiretroviral-naive. Of these 903 patients, 725 (80.3%) had been infected more than 10 years previously.

Among the 903 patients infected more than 8 years previously, 31.1% were homosexual men, 25.6% were intravenous drug users, and 33.6% were heterosexuals. There were 202 'LTNP' patients (22.3%), with a CD4 cell count nadir above 500/μl; and 103 patients (11.4%) had a CD4 nadir above 600/μl, of whom 25 (2.8% of the 903 patients) had a positive CD4 slope and were thus 'elite LNTPs'.

Among the 725 patients infected for more than 10 years, 29.9% were homosexual men, 29.5% were intravenous drug users, and 30.3% were heterosexuals. They included 101 'HIV controllers' (0.22% of the 46 880 patients), of whom 69 were 'elite controllers'.

The characteristics of the four groups are described in the Table 1, along with the characteristics of the 903 asymptomatic antiretroviral-naive patients. Median age at HIV diagnosis was 28 years in all four groups. In the immunologically defined groups, whatever the duration of HIV infection, about 70% of the patients were men, 40% were homosexual men, 24% were intravenous drug users, and 30% were heterosexuals. In the virologically defined group, 60% of the patients were men, 11% were homosexual men, more than 40% were intravenous drug users, and about 30% were heterosexuals. When multivariate logistic regression was used to identify the independent factors associated with belonging to the different groups, the only statistically significant factor was the CD4 nadir for the immunologically defined groups and

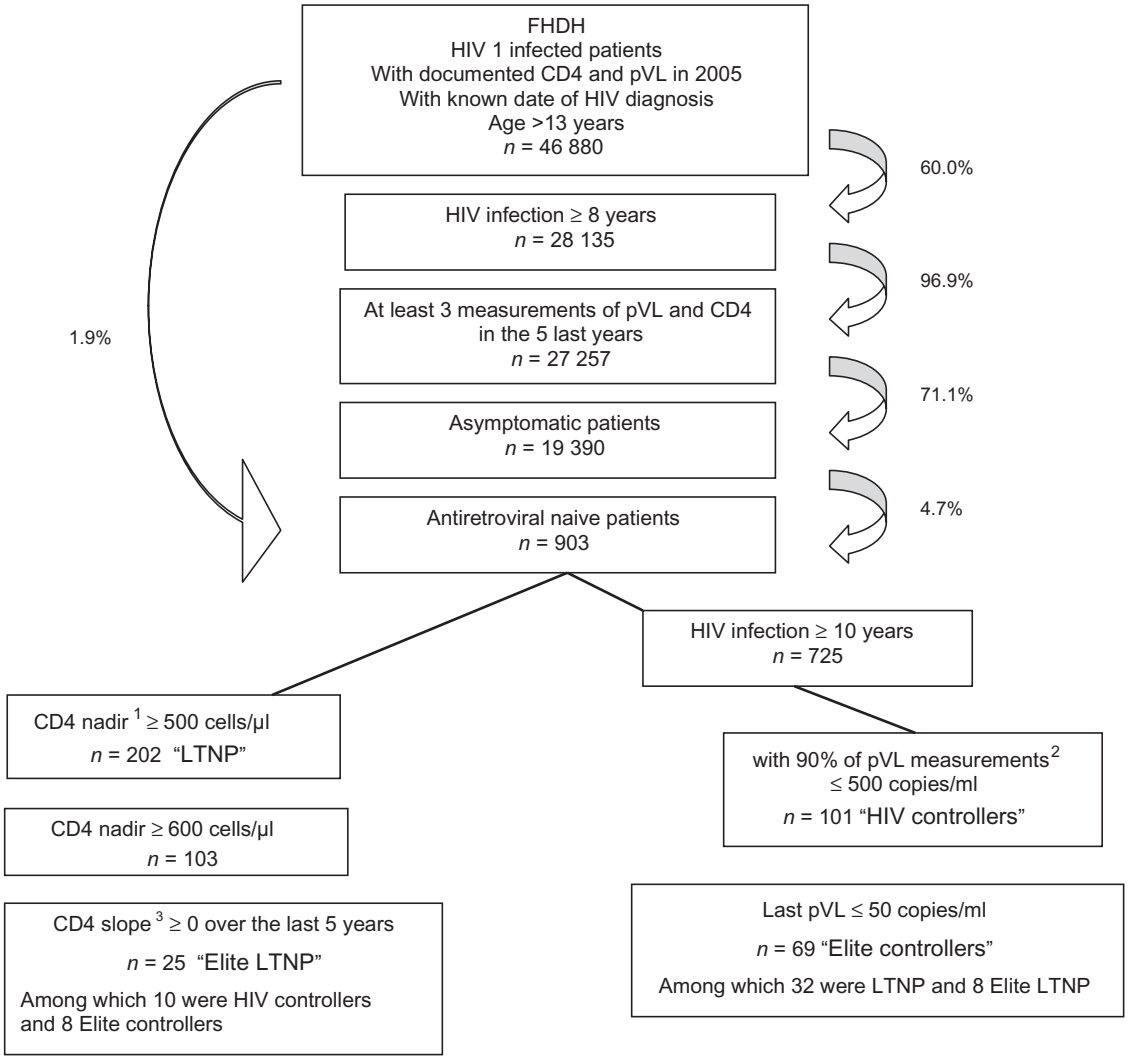

Fig. 1. Patients selection. FHDH, the French Hospital Database on HIV; IQR, interquartile range; LTNP, long-term nonprogressor; pVL, plasma viral load. [1]Established on a median of 17 (IQR: 11–25) CD4 measurements. [2]Established on a median of 14 (IQR: 9–20) pVL measurements. [3]The CD4 slope over the past 5 years is evaluated on at least three measurements of CD4 in the past 5 years before 2005, among which at least one measurement of more than 4 years.

the maximum viral load for the virologically defined groups.

As expected, the median CD4 cell nadir was higher in the immunologically defined groups (600 and 670/µl) than in the virologically defined groups (450 and 484/µl). Plasma HIV RNA levels were slightly higher in the immunologically defined groups than in the virologically defined groups. The median HIV RNA level in 2005 was 2149 copies/ml in LTNP patients and 168 copies/ml in elite LTNP patients. CD8 cell counts were available for about three-quarters of the patients. The CD4/CD8 ratio was above 1 in more than 40% of the elite LTNP patients, HIV controllers, and elite controllers, but in only 29.9% of LTNP patients and in 11.5% of the 903 patients.

Ten elite LTNP patients (40%) were also HIV controllers and eight (32%) were elite controllers (Fig. 2). In 2005, 15 elite LTNP patients (60%) had a last plasma HIV RNA value above 50 copies/ml and 11 (44%) had a last value above 500 copies/ml. Among the elite controllers, 32 (46%) were LTNP and eight (12%) were elite LTNP. In 2005, 18 (26%) of the elite controllers had a last CD4 cell count below 500/µl.

Discussion

The present study, based on one of the largest existing prospective cohorts of HIV-infected patients (more than 110 000 patients belonging to various transmission groups), confirms the very low prevalence (<0.5%) of LTNP, elite LTNP, HIV controller, and elite controller patients. This confirms previous findings [1,2,10], although the estimated prevalence was lower in our study, probably owing to the use of different definitions and/or

Table 1. Description of different groups of patients characterized in 2005 in the French Hospital Database on HIV and who were asymptomatic and therapy-naive.

	HIV infection ≥8 years			HIV infection >10 years	
	$N = 903$ patients	LTNP patients; CD4 cell count nadir ≥500/μl; $N = 202$ patients	Elite LTNP patients; CD4 cell count nadir ≥600 and CD4 slope ≥0; $N = 25$ patients	HIV controller pts; 90% of pVL measurements ≤500 copies/ml; $N = 101$ patients	Elite controller patients; 90% of pVL measurements ≤500 copies/ml and last pVL ≤50 copies/ml; $N = 69$ patients
Sex *n* (%)					
Women	323 (35.8)	68 (33.7)	7 (28.0)	40 (39.6)	26 (37.7)
Men	580 (64.2)	134 (66.3)	18 (72.0)	61 (60.4)	43 (62.3)
Transmission group *n* (%)					
Homosexual	281 (31.1)	77 (38.1)	11 (44.0)	11 (10.9)	8 (11.6)
IVDU	231 (25.6)	47 (23.3)	6 (24.0)	42 (41.6)	30 (43.5)
Heterosexual	303 (33.6)	62 (30.7)	6 (24.0)	31 (30.7)	19 (27.5)
Transfusion	32 (3.5)	5 (2.5)	1 (4.0)	11 (10.9)	8 (12.6)
Others	56 (6.2)	11 (5.4)	1 (4.0)	6 (5.9)	4 (5.8)
Geographic origin *n* (%)					
France	791 (87.6)	181 (89.6)	23 (92.0)	92 (91.1)	64 (92.8)
Sub-Saharan Africa	48 (5.3)	10 (5.0)	0 (0.0)	7 (6.9)	4 (5.8)
Other	64 (7.1)	11 (5.4)	2 (8.0)	2 (2.0)	1 (1.4)
CD4 cell count nadir until end of 2005 (/μl) median (IQR)	356 (279–479)	600 (549–686)	670 (632–722)	450 (288–632)	484 (296–671)
Maximum pVL (copies/ml) until end of 2005 median (IQR)	20100 (3560–68814)	7280 (800–32472)	1970 (500–13000)	500 (500–500)	500 (500–500)
At HIV diagnosis					
Age median (IQR)	28.2 (23.9–33.9)	28.6 (24.7–33.9)	27.8 (24.2–30.5)	27.9 (24.4–35.3)	27.9 (24.4–35.6)
Year of HIV diagnosis median (IQR)	1992 (1988–1995)	1992 (1989–1995)	1991 (1988–1994)	1990 (1986–1993)	1990 (1987–1994)
At FHDH enrolment					
Age median (IQR)	32.9 (28.2–38.8)	33.9 (28.8–38.7)	34.8 (29.0–36.7)	34.2 (29.2–41.1)	34.9 (29.6–41.7)
CD4 cell count (/μl) median (IQR)	632 (483–827)	858 (717–1070)	852 (738–975)	729 (539–926)	740 (524–939)
pVL (copies/ml)					
Missing *n* (%)	379 (42.0)	99 (49.0)	11 (44.0)	67 (66.6)	43 (62.3)
Median (IQR)	2609 (500–10000)	7961 (500–4500)	665 (500–10000)	500 (68–500)	500 (50–500)
In 2005 (last follow-up visit)					
Age median (IQR)	42.9 (38.5–47.5)	42.5 (39.2–47.5)	42.2 (39.8–45.3)	44.5 (41.0–50.0)	44.5 (40.9–48.5)
CD4 cell count (/μl) median (IQR)	473 (359–634)	759 (635–912)	946 (871–946)	661 (490–888)	721 (495–912)
pVL (copies/ml) median (IQR)	5872 (646–28700)	2149 (132–15900)	168 (50–5868)	50 (50–139)	50 (50–50)
≤50 copies/ml *n* (%)	106 (11.7)	45 (22.3)	10 (40.0)	69 (68.3)	69 (100.0)
≤500 copies/ml *n* (%)	210 (23.2)	76 (37.6)	14 (56.0)	99 (98.0)	69 (100.0)
CD8 cell count (/μl)					
Missing *n* (%)	222 (24.6)	55 (27.3)	7 (28.0)	29 (28.7)	18 (26.1)
Median (IQR)	970 (697–1345)	1045 (747–1560)	1091 (888–1275)	808 (630–1250)	817 (562–1119)
CD4/CD8 median (IQR)	0.5 (0.3–0.7)	0.8 (0.5–1.1)	0.9 (0.8–1.2)	0.9 (0.6 –1.3)	0.9 (0.7–1.4)
CD4/CD8 ≥1 *n* (% among patients with available CD8)	78 (11.5)	44 (29.9)	8 (44.4)	29 (40.3)	24 (47.1)

IQR, interquartile range; FHDH, French Hospital Database on HIV; IVDU, intravenous drug user; LTNP, long-term nonprogressor; pVL, plasma viral load.

denominators. Indeed, estimates of the prevalence of these different phenotypes are highly dependent both on the history of HIV epidemics and on changes in ART practices and indications. Among the criteria used for initial patient selection in our study (HIV infection ≥8 years, at least three plasma HIV RNA and CD4 cell values, no clinical signs or symptoms, and no ART), treatment-naive status was by far the most selective. Only 4.7% of the 19 390 asymptomatic patients who had been infected for more than 8 years and who had available CD4 cell and HIV RNA values were still antiretroviral-naive. These patients represented 1.9% of the initial 46 880 patients.

Patients belonging to all transmission groups can remain asymptomatic and antiretroviral-naive. However, patients differed markedly depending on whether they were identified on the basis of immunologic parameters (LTNP and elite LTNP patients) or viral parameters (HIV/elite controllers). About 40% of the immunologically defined patients were homosexuals and one-quarter were intravenous drug users, whereas in the virologically defined group less than 15% of patients were homosexuals and 40% were drug users. There is no clear explanation for this difference. It might be due to the patient selection process, which included the use of ART. Indeed, many

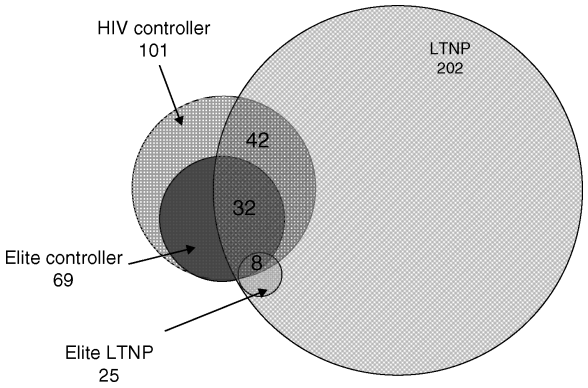

Fig. 2. Overlap among the four groups of patients with slow disease progression in the French Hospital Database on HIV. The number indicates the number of patients in each group. LTNP, long-term nonprogressor.

studies have shown that, relative to other transmission groups, homosexual patients are more likely to seek and to receive ART and that they start treatment at higher CD4 cell counts; in contrast, intravenous drug users are more likely to have delayed access to care [11–13]. The difference might also be due to a higher likelihood of superinfection among homosexual patients who continue at-risk sexual practices [14].

The lack of standardized definitions of LTNP and HIV controllers hinders comparisons among studies [1,2,4,5]. Our flow chart helps to identify the most selective of the criteria used to characterize these patients. Such information might be useful for the design of future studies. It indicates, for instance, that a severe immunologic criterion such as a positive CD4 slope [2,15] over a certain period of time is more selective than a longer duration of HIV infection (10 years instead of 8 years) for selecting patients who are asymptomatic and antiretroviral-naive several years after being infected by HIV. Together with recent data [16] showing that the selection of patients with severe phenotypes enhances the chance of finding genetic signal in genome wide association studies, this indicates that study investigators should concentrate their effort in recruiting patients on the most severe criteria such as elite LTNP and elite controllers.

We found little overlap among the definitions of elite LTNP patients and HIV/elite controllers. Indeed, only 32% of elite LTNP patients were elite controllers and only 12% of elite controllers were elite LTNP patients. Although most patients in the immunologically defined groups had low HIV RNA levels, about a quarter of them had higher levels at their last visit (>16 000 copies/ml among LTNP and >6000 copies/ml among elite LTNP). The situation of these latter patients resembles that of African green monkeys or sooty mangabeys, two natural hosts of simian immunodeficiency virus (SIV). Contrary to Asian monkeys (macaques), SIV is typically non-pathogenic in these monkeys and does not induce significant $CD4^+$ T-cell depletion, chronic T-cell activation [17,18], or AIDS, despite high-level viral replication in plasma and the gut. Persistent immune activation plays a central role in CD4 T-cell depletion and progression to AIDS in both HIV and SIV infection [19] and may be an independent predictor of disease progression in untreated patients [20,21]. Choudhary *et al.* [22] studied three LTNP patients with high plasma viral load and found low levels of immune activation, similar to those of LTNP patients with low plasma viral load. In addition, it has recently been reported that HIV controllers may, unexpectedly, have higher levels of T-cell activation than patients on effective cART. This may contribute to gradual CD4 T-cell loss even in the absence of measurable viremia [23]. Thus, the level of immune activation may be relatively high in elite HIV controllers with CD4 T-cell loss and low in elite LTNP patients with active viral replication.

The mechanisms by which CD4 cells are not depleted and viral replication is controlled are unclear [9,24]. Both viral factors and host genetic factors such as human leucocyte antigen (HLA) class I alleles may play a role. Indeed, recent studies show that HLA-B27 is associated with efficient polyfunctional CD8 responses [25] and that HLA-B57 is associated with viral control [26]. Characterization of clinical phenotypes is important to drive future genomic studies. Genome-wide approaches designed to identify determinants of nonprogression are ongoing in the GISHEAL collaborative project (Genetic and Immunological Studies of European and African HIV-1+ Long Term Non-Progressors) [27] for LTNP patients and in the HIV Controller Consortium [8] for elite controllers. Such analyses will show whether the two forms of 'resistance' – virologic and immunologic – have different genomic substrates.

Conclusion

Three particular groups of patients may hold keys to successful HIV vaccine development, namely viremic 'elite' LTNPs, 'elite' viral controllers with CD4 cell depletion, and patients with viral control and stable CD4 cell counts.

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