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Abstract

The French Hospital Database on HIV (FHDH) is a hospital-based multicentre open cohort with inclusions ongoing since 1989. The research objectives focus mainly on mid- and long-term clinical outcomes and therapeutic strategies, as well as severe AIDS and non-AIDS morbidities, and public health issues relative to HIV infection. FHDH also serves to describe HIV-infected patients receiving hospital care in France. FHDH includes data on more than 120 000 HIV-infected patients from 70 French general or university hospitals distributed throughout France. Patients are eligible for inclusion if they are infected by HIV-1 or HIV-2 and give their written informed consent. Standardized variables are collected at each outpatient visit or hospital admission during which a new clinical manifestation is diagnosed, a new treatment is prescribed or a change in biological markers is noted, and/or at least every 6 months. Since its inception, variables collected in FHDH include demographic characteristics, HIV-related biological markers, the date and type of

AIDS and non AIDS-defining events, antiretroviral treatments and the date and causes of death, as reported in the medical records. Since 2005, data have also been collected on: co-infection with hepatitis B or C virus; alcohol and tobacco use; and non HIV-related biomarkers. Anyone can submit a research project by completing a standardized form available on the FHDH website (http://www.ccde.fr/_fold/fl-1385734776-429.pdf) or from the corresponding author, describing the context and objectives of the study. All projects are reviewed by the scientific committee.

Key words: HIV, cohort, FHDH, AIDS, antiretroviral treatment, comorbidities

Key Messages

- Both immunological and virological responses are useful for monitoring the response to antiretroviral treatment.
- Even moderate immunodeficiency (between 350 and 500 CD4 T cells/mm^3) is a major determinant of both AIDS-defining cancers (non-Hodgkin lymphoma, Kaposi sarcoma and cervical cancer) and non AIDS-defining cancers (lung and liver cancers and Hodgkin's lymphoma), studied separately.
- The risk of myocardial infarction is higher in HIV-infected patients exposed to protease inhibitors than in the general population, and is associated with traditional risk factors, cumulative exposure to protease inhibitors, and HIV-related parameters.

Why was the cohort set up? What was the rationale for setting up the cohort, including the original research?

History of FHDH

The French Hospital Database on HIV (FHDH) was created in 1992, following a pilot project initiated in 1989, with the aim of collecting clinical information on HIV-infected patients managed in reference HIV treatment and information centres (CISIH: Centres d'Information et de Soins de l'Immunodéficience Humaine), created by the French Ministry of Health in 1987. FHDH is a hospital-based multicentre open cohort with inclusions ongoing since 1989. The French Ministry of Health funds technical research assistants who devote half their time to clinical research and the other half to FHDH data collection in the participating centres. The data collected are used to describe HIV-infected patients receiving hospital care in France, as well as HIV disease outcomes and their determinants, including antiretroviral treatment (ART).

FHDH nowadays

With the arrival of protease-inhibitor-based combined antiretroviral therapy (cART) in March 1996 and the resulting dramatic decrease in morbidity and mortality due to all opportunistic diseases,[1,2] the HIV/AIDS epidemic has been profoundly modified over the past 17 years. FHDH research objectives now focus on three main themes: (i) mid- and long-term clinical outcomes and therapeutic strategies, including comparative effectiveness research based on propensity scores or marginal structural models; (ii) severe AIDS and non-AIDS events, including malignancies and cardiovascular disease, based on comorbidities recorded since the creation of FHDH; and (iii) public health issues relative to HIV infection, such as late access to care, retention in care and the influence of geographical origin on outcome. Because FHDH is representative of HIV-infected patients under care in France in terms of sex, age and geographical origin,[3,4] and as ART can only be prescribed and modified by hospital clinicians, FHDH can also be used to describe HIV-infected patients under care in France.[5–7] Finally, FHDH is regularly used to conduct post-marketing studies of ART drugs. It can also be used to estimate the financial costs of care, as in France the cost of HIV infection is mainly driven by the cost of antiretroviral drugs and hospitalizations, respectively 62% and 31% of the total cost.[8] The FHDH project was approved by the French computer watchdog authority (CNIL) on 27 November 1991 (*Journal Officiel*, 17 January 1992).

FHDH network

The FHDH network is composed of clinical centres and a statistical data centre that coordinates the cohort. The

governing body is the scientific committee (see Appendix 1, available as Supplementary data at *IJE* online). Since its creation, FHDH has been supported by INSERM (French National Institute of Health and Medical Research) and the French Ministry of Health. It became an ANRS (French National Agency for Research on AIDS and Viral Hepatitis) cohort (CO4) in 1996.

Who is in the cohort?

FHDH now includes data from 70 general or university hospitals distributed in the 21/26 French regions including overseas departments, with the exception of Aquitaine, Picardie, Poitou-Charentes, Limousin and Corse (Figure 1). Patients are eligible for inclusion if they are infected by HIV-1 or HIV-2 and give their written informed consent. The database is updated twice a year. Data submitted by the participating centres to the data centre are anonymized on the basis of the patient's last name, first name, and day and month of birth,[9] then encrypted. Because of the need to return to the patients' medical records to validate a diagnosis or to collect additional data for specific research projects, CNIL approval for a local correspondence list was obtained in 1999.

The database included data on 120 542 HIV-infected patients seen at least once between 1 January 1992 and 31 December 2009, with a median follow-up of 5.6 years [interquartile range (IQR) = 2.1–11.3]. The number of patients under follow-up increased by a factor of 2.5 between 1993 and 2009, because of both new diagnoses of HIV infection and prolonged survival (Table 1). The patients included in FHDH represented 56% of all patients newly diagnosed with AIDS in France between 2004 and 2006.[4] HIV-infected patients, like other patients with chronic illnesses [ALD: affection de longue durée (long-term diseases)], are eligible for 100% coverage of their healthcare costs, with no co-payments. FHDH patients represented 53% of all patients qualifying for ALD because of HIV/AIDS in 2009. As shown in Table 1, the HIV/AIDS epidemic has changed over the years, with increasing proportions of patients over 60 years of age (2.3% in 1993 vs 9.3% in 2009) and patients (especially women) from

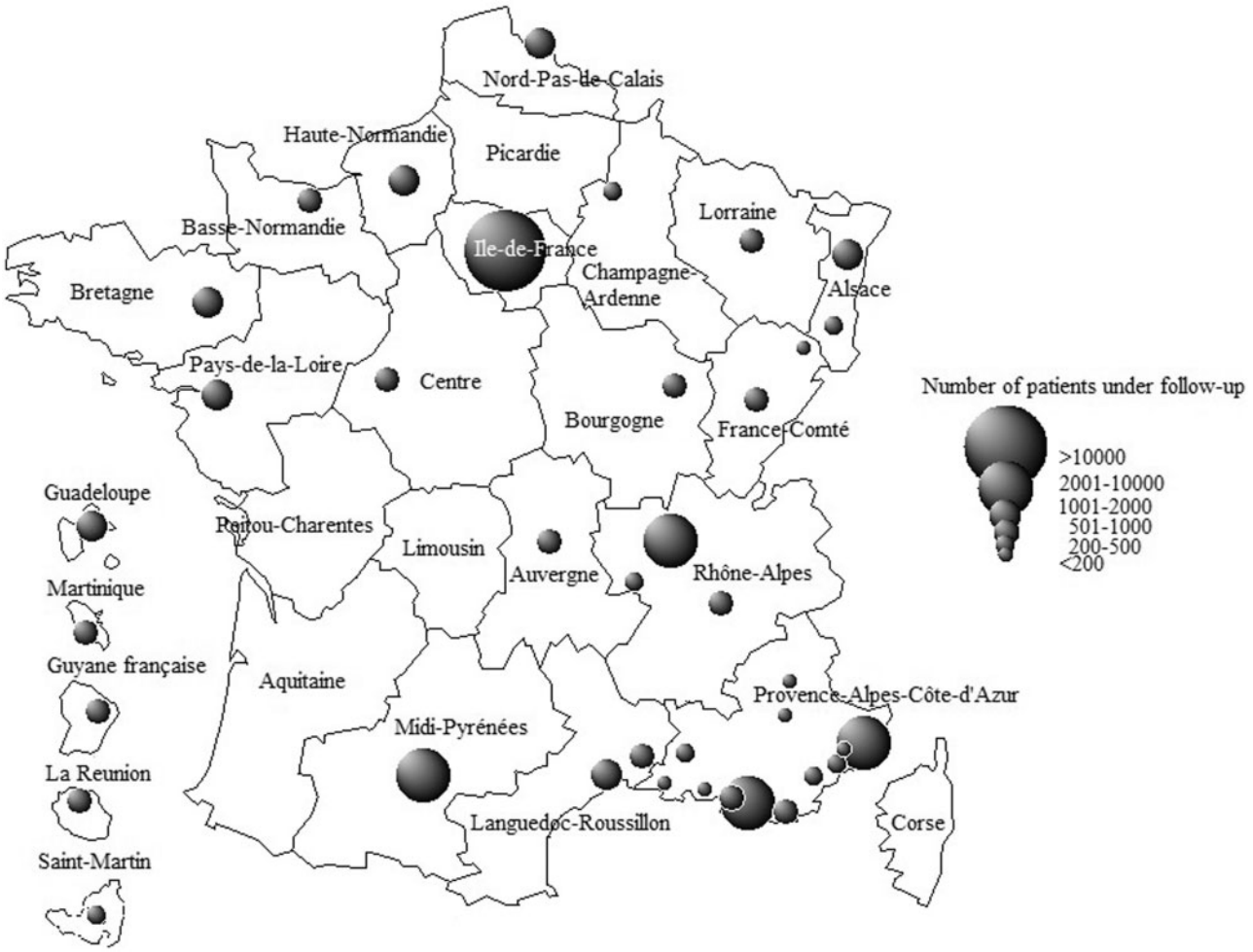

Figure 1. Regional map of FHDH participating centres, and number of patients followed in each centre in 2009. (a) France, (b) Paris area

(continued)

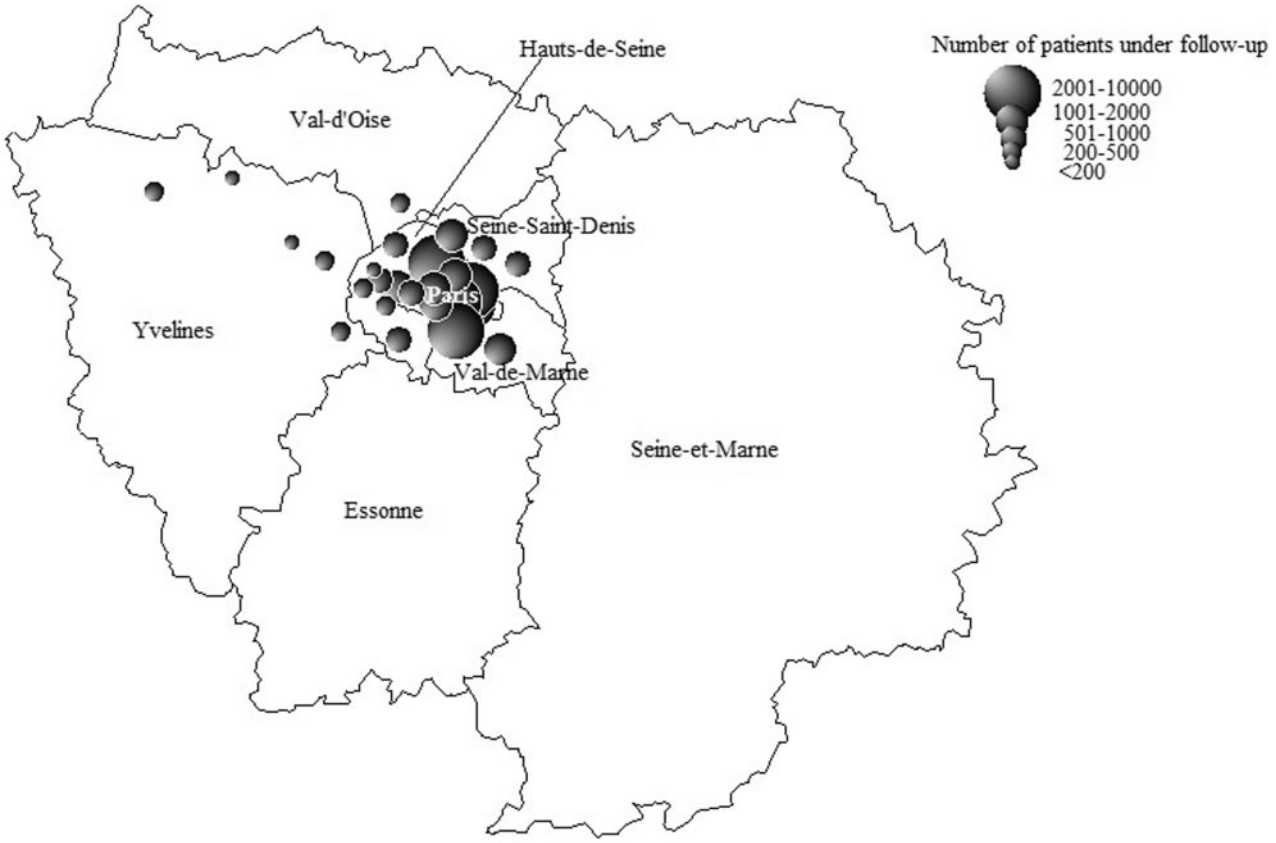

Figure 1. Continued

sub-Saharan Africa (1.9% in 1993 vs 9.2% in 2009 among men, 5.7% in 1993 vs 31.9% in 2009 among women). Cohort uptake of cART was rapid, reaching 51.6% of patients in 1997 and 85.2% in 2009. In parallel, the proportion of patients with undetectable viral load also increased, even when the 50 copies/ml cutoff was used (Figure 2). As the risk of death among patients with CD4 cell counts $>500/mm^3$ is similar to that of the general population,[10,11] having CD4 cell count $>500/mm^3$ is an indicator of immunological success. The proportion of patients with such CD4 cell counts is also rising over time as well as the proportion of patients with a normal ratio CD4/CD8, that is ≥ 1, despite the fact that this latter proportion remains relatively small, indicating an incomplete immune recovery. Soon after the advent of cART, the percentage of newly enrolled patients who were already at advanced stages of HIV infection (AIDS or CD4 $<200/mm^3$) fell by 14% between 1993 and 1997 (from 51% to 37%), whereas it only fell by 8% between 1997 and 2009 (from 37% to 29%) (Table 1).

How often have they been followed up?

Data are collected prospectively by trained research assistants, using either dedicated software provided by the French Ministry of Health, or computerized medical records. Standardized variables are collected at each outpatient visit or hospital admission during which a new clinical manifestation is diagnosed, a new treatment is prescribed or a change in biological markers is noted, and/or at least every 6 months. The observed median interval between two consecutive CD4 cell counts is 2.9 months (IQR = 1.8–4.1).

Losses to follow-up

The mid-2006 FHDH update showed that 7.5% of the patients seen in 1999 had been lost to follow-up, as defined by 12 months with no contact; 2.1% of these patients subsequently returned for follow-up (median 3.5 years without follow-up in an FHDH centre). Finally, only 5.4% had no further FHDH contacts whatsoever; 29.8% of these latter patients had died, according to a joined analysis of the Mortalité 2000 study, FHDH and CépiDC databases.[12]

What has been measured?

Since the creation of FHDH, collected baseline variables have included date of birth, gender, geographical origin, transmission group, height, date of primary infection

Table 1. Characteristics of the FHDH-ANRS CO4 cohort population according to year of follow-up and number of patients in that year

Characteristic	1993 22 208[a]	1997 37 989[a]	2001 45 999[a]	2005 54 471[a]	2009 56 458[a]
Gender (%)					
Female	25.0	27.6	29.7	32.5	33.2
Male	75.0	72.4	70.3	67.5	66.8
Origin (%)					
Male	($n = 16\,664$)	($n = 27\,510$)	($n = 32\,359$)	($n = 36\,761$)	($n = 37\,704$)
France	94.3	92.0	88.6	85.4	82.8
Sub-Saharan Africa	1.9	3.0	5.1	7.2	9.2
Other	3.8	5.0	6.3	7.4	8.0
Female	($n = 5\,544$)	($n = 10\,479$)	($n = 13\,640$)	($n = 17\,710$)	($n = 18\,754$)
France	88.8	82.6	72.9	64.6	60.3
Sub-Saharan Africa	5.7	10.0	18.4	25.9	31.9
Other	5.7	7.4	8.7	9.5	7.8
Age (years) (%)[b]					
<15	0.7	0.6	0.3	0.3	0.2
15–29	26.6	15.1	9.1	7.5	6.1
30–39	46.9	52.0	43.0	30.6	22.6
40–49	17.8	22.0	31.7	40.0	41.2
50–59	5.6	7.4	11.6	15.5	20.6
≥60	2.3	2.9	4.3	6.2	9.3
Transmission group (%)					
Men who have sex with men	39.3	36.8	35.7	33.9	34.3
Intravenous drug users	28.8	23.6	17.9	13.7	11.1
Heterosexuals	23.2	30.4	37.3	45.1	45.3
Blood products	4.2	2.8	2.3	2.1	1.7
Other or unknown	4.5	6.3	6.8	7.2	7.6
HIV serology (%)					
HIV-2	0.3	0.4	0.6	0.8	0.9
HIV-1 and HIV-2	0.3	0.3	0.4	0.4	0.3
HBsAg status (%)					
Unknown	39.6	27.8	21.1	18.0	16.7
Positive	6.9	6.7	7.2	7.5	7.6
Negative	53.5	65.5	71.7	74.5	75.7
Anti-HCV antibody status (%)					
Unknown	40.1	23.6	16.8	14.7	14.0
Negative	37.9	52.8	62.4	67.7	70.3
Positive	22.0	23.6	20.8	17.6	15.7
AIDS (%)[b]	31.4	24.2	24.7	24.9	24.5
CD4 cell count (/mm^3) (%)[b]					
Missing	8.0	3.2	2.8	3.1	5.7
<200	43.8	24.0	14.8	11.1	6.6
[200–350[	19.6	27.0	20.3	21.0	14.2
[300–500[	13.5	22.3	22.5	24.5	23.2
[500–750[	10.3	17.0	24.9	26.4	30.8
≥750	4.7	6.6	14.7	13.8	19.5
Plasma HIV-1 RNA (copies/ml) (%)[b]					
Missing	NA	10.1	4.5	4.5	8.4
≤500		32.8	56.4	65.9	
≤50					67.8
]50–500]					9.2
]500–5000]		21.2	15.0	9.9	4.9
]5000–100 000]		26.9	18.6	15.4	7.6
>100 000		8.9	5.6	4.5	2.1

(Continued)

Table 1. Continued

Characteristic	1993 22 208[a]	1997 37 989[a]	2001 45 999[a]	2005 54 471[a]	2009 56 458[a]
Antiretroviral treatment (%)[b]					
Naïve	35.6	12.9	9.2	11.8	8.5
Not on treatment, but history of treatment	15.0	3.9	7.1	8.6	5.0
One nRTI alone[c]	43.0	1.1	0.5	0.2	0.1
Two nRTIs alone[c]	3.8	28.5	6.1	1.6	0.6
Combined ART[d]	0.0	51.6	76.3	77.2	85.2
Other	2.6	2.0	0.8	0.6	0.6
cART for at least 6 months (%)	0.0	44.0	71.4	73.1	80.2
Patients newly enrolled (%)	24.1	11.7	6.6	5.2	4.1
With CD4 <200/mm^3 or AIDS at inclusion (%)	50.8	36.7	40.2	34.3	28.7

[a]Number of patients: a given patient may be followed in several periods.
[b]Value at last follow-up.
[c]Nucleoside reverse transcriptase inhibitor.
[d]cART is defined as boosted protease inhibitor monotherapy whatever the protease inhibitor; dual therapy with two boosted protease inhibitors or one boosted protease inhibitor and one non nucleoside reverse transcriptase inhibitor; treatment with at least one boosted protease inhibitor; treatment with an integrase inhibitor and/or anti-CCR5 drug; treatment with three or more drugs.

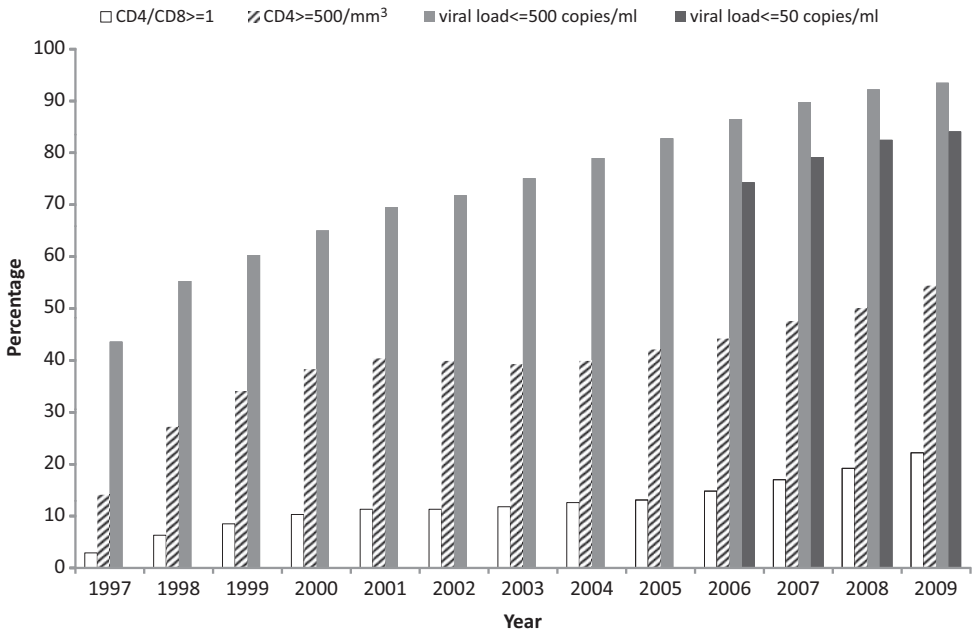

Figure 2. Yearly percentages of patients on cART for at least 6 months, either: with viral load ≤500 copies/ml or ≤50 copies/ml since 2006, when this threshold became available in all the participating centres; or with CD4 cell counts ≥500/mm^3 or with ratio CD4/CD8 ≥1

(when known) and dates of the last negative (when known) and first positive HIV tests. Variables collected at each follow-up visit include: weight; standard biological markers such as the CD4+ cell count and plasma HIV-RNA level; blood cell counts, lipids and liver enzymes; the date and type of AIDS and non-AIDS events, using the International Disease Classification;[13] antiretroviral treatments and prophylaxis of opportunistic infections; and the date and causes of death, as reported in the medical records. Since 2005, additional data have been collected on alcohol and tobacco use; serological and virological data on co-infection with hepatitis B or C virus; liver biopsy results; and non HIV-related biomarkers such as lipid levels and liver enzymes. Of note, FHDH linkage with the French deaths registry is not authorized. For all FHDH patients included in ART-CC (Antiretroviral Cohort Collaboration),[14] that

includes treatment-naïve patients initiating antiretroviral treatment with a known CD4 cell count and viral load, a panel of experts has regularly validated causes of death by using the CoDe project coding system.[15]

The statistical data centre conducts regular audits which show that AIDS-defining events and antiretroviral treatments are efficiently recorded. For research projects focusing on non AIDS-defining events, we usually return to the patients' medical records in order to collect additional data required for expert validation of diagnoses such as cancer (e.g. histology) and myocardial infarction (e.g. electrocardiogram and cardiac enzymes).

What has it found? Key findings and publications.

Between 1992 and 2012, FHDH gave rise to 132 articles published in peer-reviewed journals. A complete list of publications can be found on the FHDH website at (http://www.ccde.fr/main.php?main_file=fl-1339514221-197.html).

The first publication, dating from 1992, showed that ART was being widely prescribed to patients with CD4 cell counts below 350/mm^3 before the relevant recommendation was issued.[16] In 1999, the first collaborative study with EuroSIDA and the Swiss HIV Cohort Study was published[17] on the use of observational databases to assess the effectiveness of ART, pioneering international cohort collaborations.

Effectiveness of cART in observational studies

In a paper published in 2000,[18] we reported that, whatever the virological response 6 months after cART initiation, immunological responders had the same risk of progression to AIDS or death as solely virological responders, and that immunovirological non-responders were the most likely to progress or die. These results underlined the utility of both immunological and virological parameters for monitoring the treatment response.

More recently, we evaluated the risk of progression to AIDS or death in patients experiencing triple-class virological failure. Given the small proportion of such patients in the recent period and the need for a large sample to study clinical outcomes, the PLATO II project (Pursuing Later Treatment Option II) was conducted within COHERE, a collaboration of western European cohorts. We showed a substantial improvement in viral load suppression and an accompanying decrease in the risk of AIDS after extensive failure of the three first antiretroviral classes during the period 2000–09 within COHERE. This improvement was probably driven mainly by the availability of newer drugs with better tolerability and ease of use, and small cross-resistance profiles, suggesting the public health benefit of new drugs.[19]

Cancer trends

Since the late 1990s, the impact of cART on the risk of non AIDS-defining cancers (NADCs) has been controversial. Our study of the risk of NADCs[20] relative to the French general population showed that the relative risk of NADCs depended on the type of cancer: it was 2 for lung cancer and 30 for Hodgkin's disease, increasing slightly from 1992–95 (the pre-cART era) to 1996–99 (the cART era) [SIR = 1.39 (95% CI = 1.14–1.67)].

Several studies showed that CD4 counts at diagnosis of clinical AIDS events were higher during the cART era than before. We found that the risk of non-Hodgkin lymphoma and Hodgkin's lymphoma at a given CD4 count was similar in the pre-CART and cART eras.[21] However, the distribution of CD4 counts was different between the two periods, a higher proportion of patients having high CD4 counts in the cART era. We showed, cancer by cancer, that even moderate immunodeficiency was a major risk factor for both AIDS-defining cancers and NADCs (Figure 3).[22] This was an original finding regarding NADCs. As soon as it was published, this work was included among the evidence favouring earlier treatment initiation in both French and American guidelines.[7,23] Interestingly, the risk of anal cancer was associated with the time spent with a CD4 cell count below 200/mm^3 rather than with the count at cancer diagnosis.[22] We also found that its incidence was higher in all transmission groups in the cART era than in the pre-cART era.[24] Relative to the general population, the risk of anal cancer in HIV-infected patients was still extremely high, even in patients with current CD4 cell counts >500/mm^3 on cART.[25]

Myocardial infarction in HIV-infected patients

Soon after the advent of cART, cases of coronary artery diseases were reported and evidence emerged that protease inhibitors (PI) might increase the risk of coronary heart disease.[26–30] As early as 2003, we showed that the risk of myocardial infarction (MI) was higher in HIV-infected patients exposed to PI than in the general population and dependent on cumulative exposure (Figure 4).[31] In 2008, when a late-breaker poster at the Conference on Retroviruses and Opportunistic Infections reported a link between the risk of MI and exposure to abacavir,[32] a nucleoside analogue, we had a case-control study under way, nested within FHDH, with the aim of identifying risk factors for MI in HIV-infected patients. The European

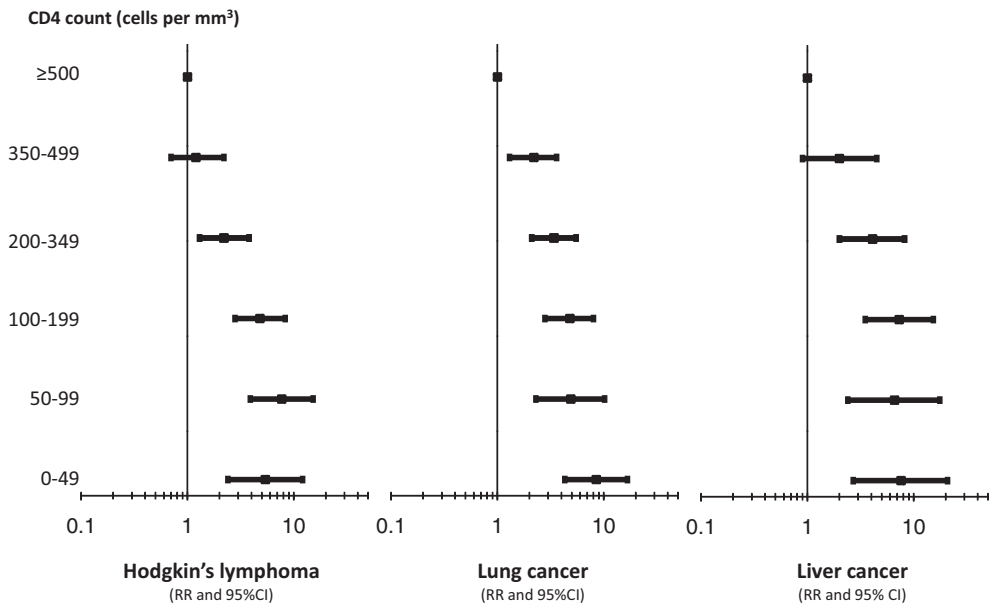

Figure 3. Relative risk [RR and 95% confidence interval (CI)] of non AIDS-defining cancers according to CD4 cell count, derived from Poisson regression model adjusted for age and CD4 cell count as time-varying covariables, for sex and exposure group, and origin[22]

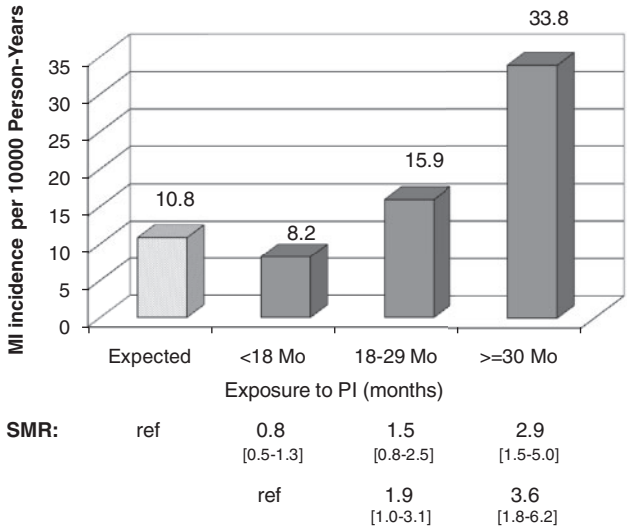

Figure 4. Incidence of myocardial infarction (MI) per 10 000 person-years among HIV-infected men exposed to protease inhibitor (PI) therapy according to the duration of exposure (in months), compared with the MI incidence expected in men in the general population of the same age.[31] The standardized morbidity ratio (SMR) is the ratio of observed cases of MI in the study group to expected cases of MI in the general population standardized on age

Medicines Agency asked us whether our study could help settle the issue of abacavir. In response, we showed that cumulative exposure to protease inhibitors was associated with an increased risk of MI, and that the link to abacavir could not be considered causal.[33] We also showed a higher risk of MI in HIV-infected patients than in the general population,[34] and the influence of both HIV replication and immunological status (CD4 nadir, current CD8 count) on the risk of MI, independently of traditional risk factors and exposure to antiretroviral drugs.[35]

Access to care, patient management and public health policy in HIV infection

We showed that late access to care (initial presentation with AIDS or CD4 <200/mm^3) was common in France between 1997 and 2002 and was associated with a higher risk of death, despite early cART initiation, for up to 4 years after the first access to hospital.[36] A computer-based simulation was used to estimate the cost-effectiveness of expanded HIV screening in France, with some model input parameters derived from FHDH.[37] We showed, in the French setting, that universal screening is economically justifiable when at least 0.1% of tested individuals are positive. These two studies were critical in the decision by the French Health Authority (HAS) to recommend expanded HIV screening in France.

We also showed that, compared with younger patients, patients over 50 years of age generally had a slower immunological response to cART and experienced more rapid clinical progression, despite a better virological response.[38]

Between January 1997 and December 2001, among treatment-naïve patients with no history of AIDS either at enrolment or during the first 3 months of follow-up, and who were prescribed cART electively, we found no influence of gender on the time to ART initiation or on the immunological response.[39] By contrast, men who have sex with men tended to start treatment at higher CD4 cell

counts and to have better immunovirological responses. This lack of gender difference in the response to ART has since been cited in US guidelines.[40]

Characterization of specific HIV-infected populations

In the context of primary infection, we observed a trend toward lower initial post-infection CD4 cell counts and higher viral loads in France between 1997 and 2005, suggesting a more rapid progression of the disease and therefore an increased HIV pathogenicity.[41] Moreover, we showed that early and prolonged cART initiated during primary infection allows long-term infection control after interruption of the initial cART in a small proportion of patients, and may have important implications in the search for a functional HIV cure.[42] Long-term non-progressor (LTNP), elite LTNP, HIV controller and elite controller patients are rare phenotypes with a prevalence of <0.5%. Elite LTNP patients are less frequent than HIV controllers (0.05% vs 0.15%, respectively).[43]

International collaborations

FHDH is part of several collaborations, including ART-CC (Antiretroviral Cohort Collaboration, since its creation in 2000),[14] EUROCOORD (NOE FP7 2011–15, including COHERE since its creation in 2005, and CASCADE since 2006) and HIV-Causal (since its creation in 2006).

Within ART-CC, we showed that, although current CD4 cell counts and HIV-1 RNA levels are the most important prognostic factors for AIDS and death, the HIV-1 RNA levels at 6 months were also prognostic for subsequent rates of AIDS.[44] The CD4 cell count is a time-dependent confounding factor when one examines the impact of treatment on clinical outcomes, as it changes over time and is associated both with the prognosis and with the decision to initiate treatment. Thus, classical multivariable models and stratified analyses may yield biased estimates of the treatment effect. Marginal structural models are one of the statistical methods used to overcome this problem. One of the main objectives of the HIV Causal collaboration is to implement this type of analysis.[45] Within ART-CC[46] and HIV Causal,[47] we took time-dependent confounding variables into account, using two different approaches, in order to determine when best to start cART. We concluded that treatment deferral until the CD4 cell count was below 350/mm^3 was associated with an increased risk of AIDS and death. French and international treatment guidelines[40] were amended to take these two papers into account, along with other findings mostly from cohort studies.

What are the main strengths and weaknesses?

The main strength of FHDH is its large size and the prospective collection of AIDS-defining events, along with non AIDS-defining events since 1989. A survey of 90 HIV cohort studies from Europe and the USA showed that, in 2007, FHDH was larger than any other single cohort or cohort collaboration (B. Ledergerber, personal communication). At a time when the incidence of all opportunistic diseases has markedly diminished, this allows us to continue to study the clinical course of HIV disease, to compare biological and clinical outcomes, to study severe non-AIDS events with sufficient statistical power and to explore methods of comparative effectiveness research.[48]

When studying non-AIDS events, we return to the medical records in order to validate the diagnoses.[24,25,33] In such studies, we often choose to use a case-control design nested within the cohort, as this overcomes the possible under-notification of non-AIDS events. For example, in our study of MI,[33] we found that 6 of 2212 patients who were initially selected as controls had a history of MI mentioned in their medical records (0.3%). The positive predictive value of diagnosis coding in the database is good. For instance, we validated 315 (89%) cases of MI among the 353 cases recorded in FHDH, and 342 (93%) of 367 diagnoses of lung cancer (ongoing project).

One weakness is the above-mentioned impossibility of FHDH linkage with the French deaths registry, meaning that deaths, particularly those from non AIDS-defining causes, may be under-recorded.[49] In addition, we do not have a specimen bank as this would have been logistically very complicated back in 1989. Likewise, we do not have drug resistance data, because it is impossible to perform extractions of the full sequences from the data management systems used in the 70 participating hospitals. Finally, socioeconomic characteristics are not currently collected, but we plan to include them from early 2015.

Can I get hold of the data? Where can I find out more?

The data remain the property of the participating centres. The scientific committee includes volunteer clinicians from the participating centres, as well as three persons from the statistical centre including the principal investigator and the coordinator of the scientific committee, and two representatives of persons living with HIV/AIDS organizations. This committee reviews submitted projects twice a year.

Anyone can submit a research project by using a standardized form available on the FHDH website to describe the context and objectives of the study. For successful applicants with adequate statistical expertise, the data can be transferred (with CNIL approval); otherwise, the FHDH statistical centre analyses the data cooperatively with the applicant. When a project is accepted by the scientific committee, a writing group is composed including the person who submitted the project, the statistician and a representative of each centre interested in the project. Further information is available on the FHDH website (http://www.ccde.fr/_fold/fl-1385734776-429.pdf) or from the corresponding author.

Supplementary Data

Supplementary data are available at *IJE* online.

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