Comparison of viro-immunological marker changes between HIV-1 and HIV-2-infected patients in France.

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Abstract

Background: HIV-2 is known to be less pathogenic than HIV-1, although the underlying mechanisms are still debated. We compared the changes over time in viro-immunologic markers in HIV-1 and HIV-2 infected patients living in France during natural history and after initiation of the first Combination of AntiRetroviral Treatment (CART).

Method: Patients were included in the ANRS CO3 HIV-1 cohort (N=6707) or the ANRS CO5 HIV-2 cohort (N=572). HIV-1 infected patients were matched to HIV-2 patients according to sex, age, HIV transmission group and period of treatment initiation. Changes in markers have been estimated with linear mixed models.

Results: Analyses were performed for three groups of patients: (1) those with estimated date of contamination (98 HIV-1 and 49 HIV-2 seroincident patients), (2) untreated seroprevalent patients (320 HIV-1 and 160 HIV-2) and (3) those who initiated a first CART (59 HIV-1 and 63 HIV-2). In group 1, CD4 T-cell decreased less rapidly in HIV-2 than HIV-1 patients (-9 vs.-49 cells/mm^3/year, $p<10^{-4}$). Estimated slopes in untreated group 2 were similar to those estimated in group 1 (-11 vs.-49 cells/mm^3/year, p=0.003). In group 3, baseline CD4 at CART initiation was not different according to the type of infection (269 vs.220 cells/mm^3). During the first two months of treatment, CD4 count increased by +59 cells/mm^3/month (95% Confidence Interval [CI]=34;84) for HIV-1 and +24 (CI=6;42) for HIV-2. The plasma viral load drop was 3-fold more important in HIV-1 patients: -1.56 log_{10}/ml/month (CI=-1.83;-1.30) vs. -0.62 (CI=-0.84;-0.40) among HIV-2 patients ($p<10^{-4}$).

Conclusion: Differences between the two infections during natural history are similar to those previously described in Africa. Paradoxically, once treatment is started, response is poorer in HIV-2 patients than in HIV-1 patients.

Keywords HIV-1, HIV-2, CD4, CD8, HIV viral load, Longitudinal study

Comparison of Viro-Immunologic Markers Changes between HIV-1 and HIV-2 Infected Patients in France from the ANRS CO 3 and CO 5 cohorts.

Short title: Comparison between HIV-1 and HIV-2 in France

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Introduction

Human Immunodeficiency Virus type 2 (HIV-2) is endemic in West Africa and sporadic in the rest of the world [1-4]. Compared to individuals infected by HIV-1, those infected by HIV-2 have a slower clinical progression [5], a lower mortality rate for patients with high CD4+ T lymphocyte count (CD4) [6-7] and lower rates of transmission [8-11]. In West African countries, comparisons have shown a slower CD4 depletion [11-13] and a lower plasma viral load in HIV-2 infected patients [13-20]. At AIDS stage, HIV-2 infected patients tend to have higher CD4 count [15] and clinical manifestations may differ between the two infections [16,17]. Several hypotheses have been raised to explain the differences between the two infections: lower virulence of HIV-2 [21,22], lower replication capacity of HIV-2 [23-27], better immune control [28-33] and lower activation of immune system during HIV-2 infection [12,23,28,34]. These factors might be associated as cell activation is linked to viral load [34]. However, cell responsiveness to activation might also vary [5,35].

All reported differences in the rate of disease progression between the two infections are from cohort studies performed in sub-Saharan Africa. No direct comparison has been made in Europe or the United States during the course of the infection, although the environment may play a role in the difference of pathogenicity between the two infections. For instance, the level of lymphocyte activation is higher in Africa than in Europe [36], consequently the role of activation in the difference between the two infections may be weaker or even reinforced because of different background rates. Therefore, we hypothesized that the differences in viro-immunologic markers levels and evolution could be different in Europe compared to sub-Saharan Africa.

Here, we report the changes in plasma HIV RNA, CD4 and CD8 over time in the French national cohort of HIV-2 infected adult patients compared to individually matched HIV-1 infected patients from the French Aquitaine Cohort.

Methods

HIV cohorts

Data is taken from the ANRS CO5 HIV-2 cohort [37] and the ANRS CO3 Aquitaine cohort [38]. The ANRS CO5 HIV-2 cohort is an ongoing national prospective study initiated in 1994 in 111 clinical centres in France. Inclusion criteria to the cohort are HIV-2 infection only, age ≥18 years, residence in France planned for at least 1 year and informed consent available. The ANRS CO3 Aquitaine cohort is an ongoing prospective study initiated in 1987.

Inclusion criteria are HIV-1 infection in patients aged over 18 years, and informed consent available. In the two cohorts, clinical, epidemiological and therapeutic data are collected by standardized questionnaires at each visit to the hospital (every 3 to 6 months according to clinical, immuno-virological and therapeutic status).

Markers quantifications

CD4 count was performed by flow cytometry in the two cohorts. Plasma HIV-1 RNA was quantified mainly by branched DNA assays (Chiron Quantiplex RNA HIV-1, Emeryville, CA, USA) with detection limits of 2.7 $\log_{10}$ copies/ml (500 copies/ml) or 1.7 $\log_{10}$ copies/ml (50 copies/ml). Although there is one commercial kit, designed for HIV-1, which can also quantify only HIV-2 subtype A RNA, there is no commercial assay specifically designed for HIV2 viral load [39]. Plasma HIV-2 RNA quantification was performed using HIV-2 strain NIHZ as a standard (Advanced Biotechnology Incorporated, Maryland, USA) with lower detection limits of either 2.4 $\log_{10}$ copies/ml (250 copies/ml) [39] or 2.0 $\log_{10}$ copies/ml (100 copies/ml) [41].

Study populations

We defined three study populations in each cohort: (1) seroincident patients, (2) seroprevalent and (3) naive patients starting a Combined Anti Retroviral Treatment (CART: combination of 2 nucleoside inhibitors and 1 protease inhibitor or 3 nucleoside inhibitors). The seroincident group included all seropositive patients whose date of seroconversion was known or well estimated, based on the period between the last negative and the first positive antibody test of less than 3 years. This population was defined retrospectively according to the availability of negative serology in the patients already included in each cohort. Data was collected from date of seroconversion and censored after 3 years of follow-up to avoid any informative dropout [42]. In this group, no patient started an antiretroviral treatment or died before the censoring date. The seroprevalent group included all seropositive untreated patients, and without documented date of HIV infection. Data was collected from inclusion and was censored if patient started an antiretroviral treatment or died. The last group included all HIV antiretroviral-naive patients who started an antiretroviral therapy consisting of at least 3 antiretroviral drugs. Data was collected from the date of first CART regimen initiation and was censored if the antiretroviral treatment was modified or if the patient died. An intent-to-continue analysis was also performed and results were similar (data not shown).

HIV-1 infected patients were individually matched to HIV-2 infected patients according to factors known to be associated with HIV-1 disease progression [38,42-44]. We considered: sex, HIV transmission group (in 4 categories: heterosexual, homosexual, blood recipients and other), period of treatment initiation (in 2 categories: 1996-2000 and 2001-2005 according to generation of available treatment) and age (in 4 categories: ≤ 30 years, 31-40, 41-50 and >50 years) at seroconversion (for group 1), at cohort inclusion (for group 2) and at first CART regimen initiation (for group 3). For each HIV-2 infected patient, one (for group 3) to two (for group 1 and 2) HIV-1 infected patients were randomly selected for matching among eligible candidates. We selected only one HIV-1 patient for each HIV-2 patient in group 3 because of the restricted number of available patients. All HIV-1 infected patients who were prescribed a non-nucleoside inhibitor in their CART regimen were excluded, this class of antiretroviral drugs being not active against HIV-2 infection [45].

We carried out two sub-analyses to account for additional factors. For group 2, in addition to sex, age and HIV transmission group, we constituted a new study population by matching for country of birth (West Africa, Europe and others). This sub-analysis was not feasible in group 1 and 3 because of the restricted number of available patients. In group 3, we performed an additional match according to the baseline plasma viral load at treatment initiation (>3.5 vs. ≤ 3.5 $\log_{10}$ copies/ml).

Statistical analysis

Changes in biological markers were studied using piecewise linear mixed models. The baseline (t = 0) was the date of seroconversion for group 1, the date of inclusion for group 2 and the date of first CART regimen initiation for group 3. Trends in the evolution of markers were fitted using one slope (in unit/year) for the first two groups. For the last group of treated patients, two slopes were considered: one for the early change (in unit/month) and a second for the long-term trend (in unit/year). The time taken for the slope to change (t = 2 months) was determined for all patients by a likelihood profile. The correlation between individual baseline value(s) and the subsequent slope(s) was handled through the unstructured covariance matrix of random effects. The left-censoring of plasma viral load due to undetectable values was taken into account using a maximum likelihood method as previously described [46]. Adjustment for the type of assay used to quantify viral load did not modify the estimates of the slopes (data not shown). Data analyses were conducted with SAS® 8.1 (SAS Institute, Cary, NC, USA).

Results

Study population

In January 2006, the ANRS CO5 HIV-2 cohort had recruited 572 patients. Of these, 89 were seroincident patients, of whom 49 were antiretroviral-naive at inclusion in the cohort (group 1). Among the 483 seroprevalent patients, 160 had no history of any antiretroviral treatment (group 2). Of the 572 patients, 105 started an antiretroviral regimen, of whom 63 received CART (group 3). By January 2006, 6 707 HIV-1 infected patients have been recruited into the ANRS CO3 Aquitaine cohort. The date of seroconversion was well estimated for 1 464 patients including 962 who were antiretroviral-naive. Among the entire cohort, 1 036 patients started the CART regimen without any previous exposure to antiretroviral. A total of 98 HIV-1 and 49 HIV-2 seroincident patients, 320 HIV-1 and 160 HIV-2 seroprevalent patients and 59 HIV-1 and 63 HIV-2 CART treated patients were included (Figure 1). Study populations are described in Table 1.

Seroincident patients

Median delay between seroconversion and first available laboratory measure was significantly shorter for HIV-1 infected patients than for HIV-2 (Table 2): 4.1 years vs. 6.8 years ($p<10^{-4}$). Without administrative censoring, the median follow-up was 36 months and 81 months for HIV-1 and HIV-2 respectively. During the first three years of follow-up, a median of four biological measurements per patient were available among HIV-1 and HIV-2 patients. The proportion of undetectable viral load measures were 14% and 85% in HIV-1 and HIV-2 infected patients, respectively. At enrolment in the cohort, median viral load was 4.11 $\log_{10}$ copies/ml for HIV-1 and 2.09 $\log_{10}$ copies/ml for HIV-2 and median CD4 count was 399 cells/mm^3 and 585 cells/mm^3 for HIV-1 and HIV-2 respectively.

Mean slopes estimated using linear mixed models were as show in table 3. CD4 count and CD4 percentage significantly decreased in the HIV-1 group (-49 cells/mm^3/year and -1.01%/year) but was quite stable in HIV-2 group (-9 cells/mm^3/year and -0.04%/year). On average, plasma viral load was quite stable over time in the HIV-1 group and in HIV-2 (-0.02 and +0.06 $\log_{10}$ copies/ml/year, respectively). CD8 count did not change significantly in both groups (Table 2). Hence, the CD4:CD8 ratio decreased significantly in HIV-1 group (-0.06/year) whereas it did not change in HIV-2 group (0.02/year, $p<10^{-4}$).

Seroprevalent patients

Median delay between inclusion into the study and the first measurement of CD4 count was 2 months for HIV-1 and 6 months for HIV-2. During the follow-up (median of 4.9 years for HIV-1 and 2.9 for HIV-2), a median of four measurements were available for HIV-1 and seven for HIV-2. At inclusion into the study, the proportion of patients with undetectable plasma viral load was 9% and 39% for HIV-1 and HIV-2 respectively.

At enrolment into the cohorts, median CD4 count was significantly lower in HIV-2 than in HIV-1 patients: 260 cells/mm^3 vs. 324 (p=0.007), probably reflecting a later enrolment of HIV-2 patients compared to HIV-1 patients. However, median plasma viral load was still significantly lower in HIV-2 (2.62 vs. 4.39 $\log_{10}$ copies/ml, $p<10^{-4}$) as well as median CD8 count (p=0.0005).

The estimated average decrease in CD4 was 4.5-fold more pronounced in HIV-1: -49 cells/mm^3/year than HIV-2: -11, (p=0.003, table 3). The CD4 percentage decrease was not significantly different between the two groups (p=0.70). There was a small insubstantial increase in plasma viral load in the two groups: +0.20 $\log_{10}$ copies/ml/year for HIV-1 and +0.14 for HIV-2. Therefore, plasma viral load was still very different in the two populations after one year of follow-up (difference of 1 $\log_{10}$ copies/ml, p=0.005). The increase in CD8 count did not differ between the two groups (p=0.44). The CD4:CD8 ratio decreased over time in the two groups, but it was more pronounced in the HIV-1 group: -0.06/year vs. -0.02 ($p=10^{-4}$). We performed a second match including country of birth as a matching variable and results were similar. In addition, we looked at any modification of the effect of the type of infection (HIV-1 or HIV-2) on the slopes of each marker according to the country of birth and none were significant.

Patients starting CART regimen

At the initiation of CART, the observed median CD4 count was not significantly different in the two groups (table 2, p=0.06), as well as CD4 percentage (p=0.70). Plasma viral load was significantly higher in the HIV-1 group ($p<10^{-4}$). During the first two months of CART, the decline in plasma viral load was 3-fold steeper in the HIV-1 group (-1.56 vs. -0.62 $\log_{10}$ copies/ml/month, $p<10^{-4}$). The increases in CD4 count and in CD4 percentage were more pronounced in the HIV-1 group (+59 cells/mm^3/month vs. +24 for HIV-2, Table 3). CD8 count was stable and did not differ significantly between the two groups (p=0.26). The CD4:CD8 ratio increased significantly in the two groups: +0.11/month for HIV-1 vs. +0.06 for HIV-2.

After the first two months of CART, in HIV-1 infected patients, CD4 count and CD4 percentage continue to increase:+46 cells/mm^3/year and +3.3%/year, respectively. Plasma HIV RNA: -1.13 log_{10} copies/ml/year and CD8 count: -100 cells/mm^3/year decreased slightly. Therefore, the CD4:CD8 ratio increased significantly: +0.16/year. In HIV-2 infected patients, all these markers were stable (Table 4). Indeed, there was no further increase in CD4 count (-2.88 cells/mm^3/year). Among the 24 (60%) patients who reached a viral load below 2.7 log_{10} copies/mL without rebound during the first 6 months of follow-up, the slope of CD4 count was also stable (+18 cells/mm^3/year, p=0.50). In the 34 (77%) HIV-1 infected patients who achieved the same viral load target, the CD4 increase was still greater (+59 cells/mm^3/year, p<0.0001).

Changes in markers were not modified according to the treatment type, i.e. with or without protease inhibitor (data not shown). In a secondary analysis, we matched patients according to plasma viral load >3.5 log_{10} copies/ml (54% of HIV-1 and 24% of HIV-2 patients) and results were similar.

Discussion

We compared the changes in viro-immunologic markers between individuals infected with HIV-2 and individuals infected with HIV-1, all being followed in France. During natural history of infection, the estimated rates of CD4+ decrease were much more pronounced in HIV-1 infected patients compared to HIV-2 infected patients. Furthermore, the estimated slopes were noticeably similar in seroprevalent and seroincident patients (-49 cells/mm^3/year for HIV-1 and -9 for HIV-2, Figure 2). The plasma viral load always remained higher in HIV-1 patients compared to HIV-2 patients with the difference varying from 1.1 $\log_{10}$ copies/ml in seroincident patients to 2.2 $\log_{10}$ copies/ml in the patients initiating CART. Differences in CD8 count mirrored to the differences in plasma viral load. Although a formal comparison with studies performed in Africa is difficult because of the great variability in the dates of enrolment since the onset of infection, reported differences in the present study look similar to those performed in Africa [12,13,18-20,23,24,26,33,47,48]. In seroprevalent cohorts of patients not treated with antiretrovirals, the reported differences in HIV RNA varied between 1.5 $\log_{10}$ and 3.3 $\log_{10}$, and between 50 and 400 cells/mm^3 for CD4 count [23,24,47,48]. The average difference of each marker between the seroincident HIV-1 and HIV-2 groups in the present study were also similar to those reported in a seroincident cohort of female sex workers in Senegal [18].

A novel aspect of this study is the estimation of slopes for each marker. Here again, these estimations were similar to those reported in Senegal [48] with a decline of 13% in T-cell count in HIV-1 infected patients (16% in [48]) and 3.7% in HIV-2 infected patients (4.1% in [48]). However, Gottlieb et al. reported similar slopes in both infections when controlling for plasma viral load levels. In our study, however, neither baseline plasma viral load (according to the following categories: <2.7, 2.7-3.7, >3.7, p=0.44) nor baseline CD4 count (<200, 200-500, >500, p=0.17) influenced the effect of either HIV-1 or -2 on CD4 slopes in seroprevalent patients. In other words, the differences in CD4 count decline between the two infections were similar whatever the viral load or CD4 count at the time of enrolment into the cohort.

The difference in pathogenicity between the two types of virus may be independent of environment because, in this study, the differences between the natural history HIV-1 and HIV-2 infection were similar for patients from the same geographic area. However, this study did not explore the respective roles of the host and the virus in determining the differences between the two infections. Whether differences in pathogenicity are mainly due to viral

replication, viral infectivity, cell susceptibility to activation, or CTL response remains unknown.

The virological response to CART was weaker in HIV-2 patients whatever the initial HIV RNA level. This result has been previously reported in Africa, Europe and the United-States [49-54]. In Abidjan (Côte d'Ivoire), Adjé-Touré et al. [51] reported a median viral load decrease of -0.6 $\log_{10}$ copies/ml and an increase of +80 cells/mm^3 for CD4 count, two months after the beginning of therapy in HIV-2 treated patients. The cause of this poor immunological response to treatment is a matter of debate [49], the first hypothesis being the limited impact of antiretroviral drugs on *in vivo* HIV-2 replication. It is difficult to distinguish whether the poorer *in vivo* response in HIV-2 patients might be linked to the potency of antiretrovirals [51,53,55] or to pathogenic features of HIV-2 infection such as the low replicative capacity [27,57]. The 50% divergence in *protease* gene nucleotides between the two types of infection could explain the reduced susceptibility of HIV-2 to the protease inhibitors developed for HIV-1 infected patients [49,57]. It is also clear that the potency against HIV-2 differs for each individual protease inhibitor [55,56] and that resistance may occur [51,58-61]. Some of these resistances are similar to those observed in HIV-1 infection [54,62] but others differs (e.g. Q151M) leading to the hypothesis that the preferred pathway for resistance development may be different between the two viruses [63]. Indeed, it could be expected that a more potent regimen leading to better virological control would improve the global response to treatment. However, the CD4 count did not increase in response to treatment in HIV-2 patients with controlled viral load during the first 6 months. It should also be noted that HIV-2 patients started an antiretroviral treatment at the same CD4 count as than HIV-1 patients, so they started therapy after a longer duration of infection. This late initiation of antiretroviral therapy in HIV-2 infection might contribute to the poorer response to treatment in particular in the CD4 increase. Hence, the findings of the present study are in favour of an earlier initiation of HAART treatment in HIV-2 infected patients.

Several limits of this study should be recognized. First, the individual matching was limited to a restricted number of potential confounding factors. We were not able to match for country of birth in all analyses because of the restricted number of patients from West Africa in the Aquitaine cohort. However, we could perform such matching for the seroprevalent group and results were similar. Another limitation was the censoring of follow-up due to change in treatment or death. This may lead to biased estimates of the change in viro-immunological markers. However, the consistency in the estimates of the slopes for each marker between the seroprevalent and seroincident groups, although the censoring was only

administrative for this latter group (three years of follow-up), argues in favour of the validity of estimates. Finally, the large number of HIV-2 infected patients with undetectable viral load yielded to insufficient information to reliably estimate the slopes. Therefore, blunted variations in HIV RNA viral load (lower than the usual measurement of 0.5 $\log_{10}$ copies/ml) need to be explored with more sensitive assays.

In conclusion, this study, the first comparing the evolution of markers between HIV-1 and HIV-2 infected patients outside of Africa, found similar differences between the two infections in Europe and in Sub-Saharan Africa. Although the difference in viral load is consistent across all analyses, the biological mechanism is still a matter of debate. The reduced response to CART in HIV-2 infected patients raises the question of optimal antiretroviral drug regimens and the right time to initiate treatment in HIV-2 infection. A better understanding of the differences in pathogenicity between the two infections may lead to improvements in treating both of them.

Appendix

Composition of the ANRS CO3 Aquitaine cohort:
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Table 1: Characteristics of patients from ANRS CO 3 Aquitaine and ANRS CO 5 HIV-2 cohorts according to the study group

Characteristics		Seroincident group		Seroprevalent group		Naive starting CART	
		HIV-1	HIV-2	HIV-1	HIV-2	HIV-1	HIV-2
Total		98	49	320	160	59	63
Sex	Male	26	13	128	64	27	28
	Female	72	36	192	96	32	35
Age*	≤ 30	48	24	250	125	6	6
	30-40	30	15	70	35	14	14
	40-50	18	9	0	0	21	25
	> 50	2	1	0	0	18	18
HIV transmission group	Heterosexual	52	26	286	143	52	54
	Blood recipients	36	18	0	0	2	4
	Homosexual	4	2	10	5	2	2
	Other	6	3	24	12	3	3
Country of birth	Europe	92	10	292	55	49	12
	West Africa	0	32	6	96	2	43
	Other	6	7	22	9	6	8
Year of first CART initiation	1996-1999	-	-	-	-	9	9
	2000-2005	-	-	-	-	50	54
First CART including PI		-	-	-	-	37	37
	Ritonavir	-	-	-	-	4	1
	Ritonavir + Lopinavir	-	-	-	-	9	13
	Ritonavir + Indinavir	-	-	-	-	0	8
	Ritonavir + Saquinavir	-	-	-	-	2	2
	Ritonavir + Telzir	-	-	-	-	1	1
	Nelfinavir	-	-	-	-	9	10
	Indinavir	-	-	-	-	7	1
	Saquinavir	-	-	-	-	1	0
	Atazanavir	-	-	-	-	4	0
	Lopinavir	-	-	-	-	0	1

* at seroconversion for seroincident patients, at inclusion for seroprevalent patients and at first CART regimen initiation for patients starting CART

Table 2: Characteristics at enrolment into the cohorts and at the time of treatment initiation of patients from ANRS CO 3 Aquitaine and ANRS CO 5 HIV-2 cohorts according to the study group

Characteristics		Seroincident patients		Seroprevalent patients		Naive starting CART	
		HIV-1 (n=98)	HIV-2 (n=49)	HIV-1 (n=320)	HIV-2 (n=160)	HIV-1 (n=59)	HIV-2 (n=63)
Median delay between seroconversion and baseline (years) (IQR*)		4.1 (2.0-6.9)	6.8 (3.6-14.2)	-	-	-	-
Median CD4 cell count /**mm^3** (IQR)		399 (229-605)	585 [a] (458-838)	324 (172-503)	260 [b] (116-421)	277 (141-370)	267 (163-381)
CD4 cell count (%)	>500	40 (42)	31 (63)	81 (25)	21 (16)	7 (12)	5 (8)
	350-500	19 (20)	11 (22)	60 (19)	23 (18)	6 (10)	16 (25)
	<350	37 (38)	7 (15)	179 (56)	85 (66)	44 (78)	42 (67)
Median CD4% (IQR)		21.6 (12.6-32.6)	37.0 [a] (28.0-43.0)	15. (7.0-23.3)	20.0 [b] (10.0-28.5)	17.8 (12.0-22.6)	15.0 (12.0-25.5)
Median CD8 cell count/mm^3 (IQR)		842 (631-1 116)	621[a] (484-830)	788 (527-1 219)	696 [b] (461-993)	883 (580-1 202)	670 [a] (376-853)
CD8 cell count (%)	>1 000	34 (35)	7 (14)	111 (35)	30 (23)	18 (32)	7 (13)
	≤1 000	64 (35)	42 (86)	209 (35)	99 (77)	39 (68)	46 (87)
Median CD4/CD8 ratio		0.45 (0.25-0.71)	1.05 [a] (0.62-1.42)	0.37 (0.20-0.58)	0.36 (0.15-0.68)	0.27 (0.17-0.42)	0.31 (0.23-0.54)
CD4/CD8 ratio (%)	≥1	16 (16)	26 (53)	25 (8)	14 (12)	1 (2)	4 (7)
	<1	82 (84)	23 (47)	295 (92)	115 (98)	56 (98)	49 (93)
Median viral load $\log_{10}$ cp/ml (IQR)		4.11 (3.60-4.55)	2.40 [a] (2.00-2.40)	4.40 (3.75-5.10)	2.62 [a] (2.40-3.68)	4.64 (3.01-5.18)	2.92 [a] (2.40-3.72)
Viral load (%)	≤2.7	2 (7)	41 (89)	8 (8)	70 (54)	10 (17)	21 (34)
	>2.7	27 (93)	5 (11)	98 (92)	59 (46)	47 (83)	42 (66)

* IQR: InterQuartile Range

Comparison between HIV-1 and HIV-2, (a) p-value $<10^{-4}$, (b) p-value <0.001

Table 3: Estimated mean (95% Confidence Interval) slopes by year from linear mixed models for seroincident and seroprevalent patients from ANRS CO 3 Aquitaine and ANRS CO 5 HIV-2 cohorts

	Seroincident patients			**Seroprevalent patients**		
	HIV-1 (N=98)	HIV-2 (N=49)	p-value*	HIV-1 (N=320)	HIV-2 (N=160)	p-value*
Change in CD4 cell count/mm^3	-49 (-60;-38)	-9 (-18;1)	$<10^{-4}$	-49 (-60;-41)	-11 (-18;-3)	0.0018
Change in CD4 (%)	-1.01 (-1.95;-0.07)	-0.04 (-0.41;0.33)	0.004	-0.92 (-1.45;-0.40)	-0.58 (-0.95;-0.22)	0.11
Change in viral load in $\log_{10}$ cp/ml	-0.02 (-0.19;0.14)	0.06 (0.05;0.08)	0.87	0.20 (0.13;0.28)	0.14 (0.09;0.18)	$<10^{-4}$
Change in CD8 cell count/mm^3	-5 (-33;23)	-8 (-20;3)	0.46	12 (-6;31)	17 (1;33)	0.44
Change in CD4/CD8 ratio	-0.06 (-0.08;-0.04)	0.02 (-0.00;0.04)	$<10^{-4}$	-0.06 (-0.07;-0.04)	-0.02 (-0.03;-0.00)	10^{-4}

* Comparison between HIV-1 and HIV-2

Table 4: Estimated mean (95% Confidence Interval) slopes from linear mixed models for patients starting CART from ANRS CO 3 Aquitaine and ANRS CO 5 HIV-2 cohorts

		naive starting CART		
		HIV-1 (N=59)	HIV-2 (N=63)	p-value*
Slope during the first two months	CD4 cell count/mm^3/month	60 (34;84)	25 (7;42)	0.06
	CD4%/month	3.19 (2.18;4.21)	1.25 (-0.62;3.12)	0.11
	Viral load in $\log_{10}$ cp/ml/month	-1.56 (-1.83;-1.30)	-0.62 (-0.84;-0.40)	$<10^{-4}$
	CD8 cell count/mm^3/month	-51 (-109;6)	2 (-70;73)	0.26
	CD4/CD8 ratio/month	0.11 (0.06 ;0.15)	0.06 (0.02;0.10)	0.22
Slope after the first two months	CD4 cell count/mm^3/year	46 (8;84)	-3 (-38;32)	$<10^{-4}$
	CD4%/year	3.29 (1.38;5.19)	0.39 (-2.55;3.33)	0.02
	Viral load in $\log_{10}$ cp/ml/year	-1.13 (-2.35;0.09)	0.02 (-0.27;0.32)	0.42
	CD8 cell count/mm^3/year	-100 (-183;17)	1 (-101;104)	0.08
	CD4/CD8 ratio/year	0.16 (0.07;0.25)	-0.02 (-0.11;0.06)	0.004

* Comparison between HIV-1 and HIV-2

Figure 1: Selection of the 3 studied groups from ANRS CO 3 Aquitaine and ANRS CO 5 HIV-2 cohorts.

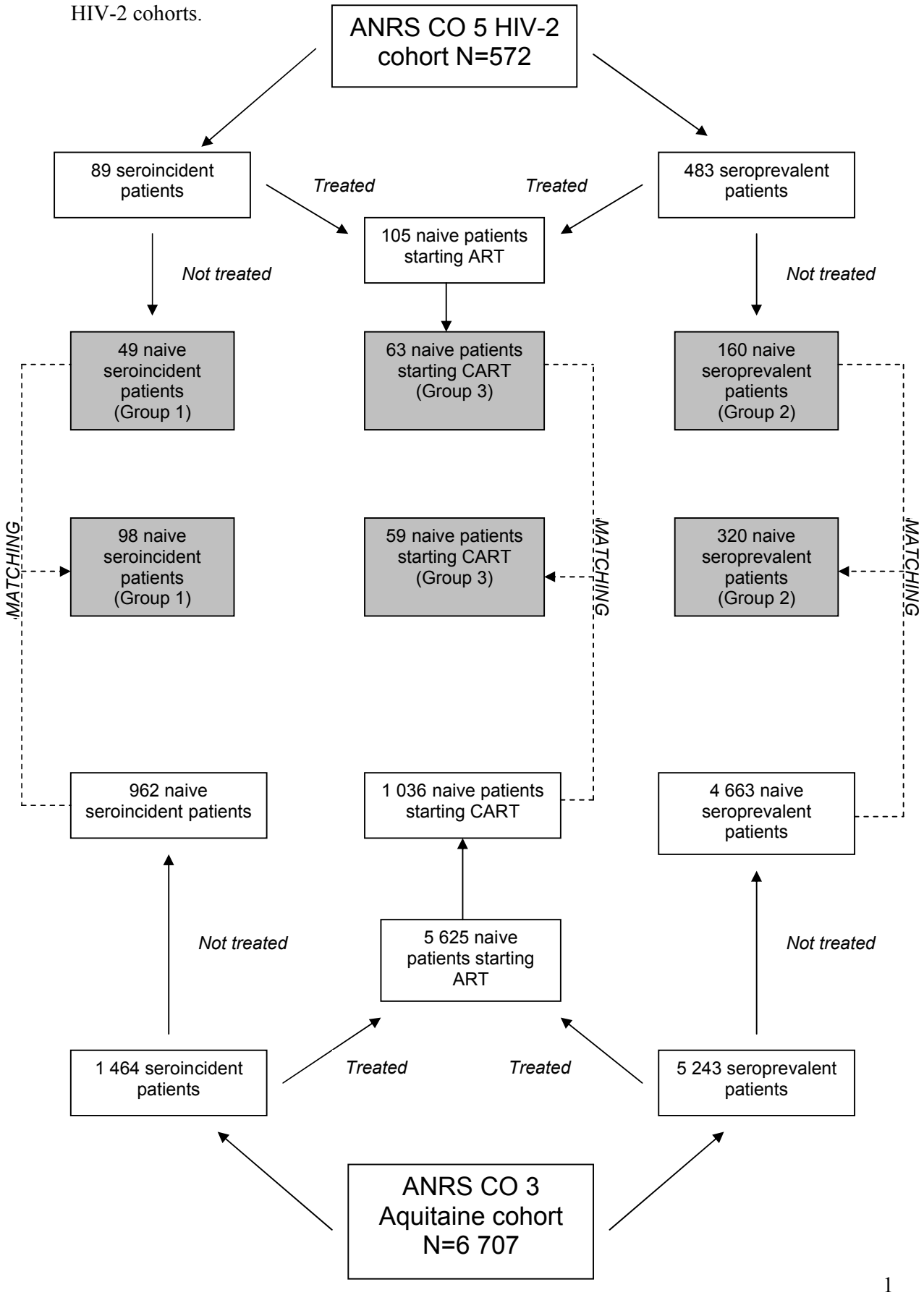

Figure 2: Estimated mean (95% Confidence Interval) CD4 T-cell slopes (cells/mm^3/year for seroincident, seroprevalent and 2nde slope of naive starting CART patients and cells/mm^3/month for 1^{rst} slope) for seroincident, seroprevalent and naive starting CART patients from ANRS CO 3 Aquitaine and ANRS CO 5 HIV-2 cohorts.