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HIV-1 X4/R5 co-receptor in viral reservoir during suppressive HAART

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As immune recovery during HAART is mainly caused by the expansion of X4-naive cells, we studied the evolution of HIV tropism in the reservoir of 34 patients receiving 48 weeks of HAART. No change in virus tropism was observed over time, but patients with X4 viruses had higher HIV-1 proviral DNA levels than patients with R5 viruses. This suggests that CCR5 antagonist activity should not be compromised in patients harbouring R5 viruses before starting HAART.

The restoration of CD4 T cells in response to HAART depends on a slow increase in naive CD4 T cells [1]. Naive CD4 T cells could be a significant HIV reservoir in patients harbouring X4 variants perhaps because these cells almost exclusively bear the X4 co-receptor [2,3].

A relationship between co-receptor use and HIV disease progression has been established [4], but the impact of an effective HAART regimen on HIV-1 tropism is not completely understood. The potential influence of HAART on the selection of X4 viruses has been underlined in a study on 28 HIV-1 subtype C-infected patients describing the emergence of X4 viruses associated with the use of HAART [5]. A switch from R5 to X4 variants was found in a longitudinal follow-up of patients under 5 years HAART, but other studies suggested that HAART might delay the selection of X4 viruses [6–8]. Moreover, the X4 viruses could play a role in the pathogenesis of poor immune reconstitution on HAART [9]. Those previous studies raised the question of the risk of improving the reservoir with X4 viruses in patients under HAART and harbouring an immune reconstitution, because there is still a debate about the existence of persistent low viral replication under HAART [10]. This could have an impact on the use of CCR5 antagonists, such as maraviroc and vicriviroc, which block HIV entry into the cell and are particularly active against HIV-1 R5 strains. In maraviroc clinical trials, the emergence of X4 viruses has been described in some patients [4,11,12]. Phylogenic analysis indicated that the X4-using variants probably emerge from a pre-existing X4-using reservoir, rather than via co-receptor switch of R5 tropic clones under maraviroc selection pressure. It is thus important to determine HIV tropism in the reservoir during HAART to know whether CCR5 antagonists can still be effective after months of HAART. The objectives of this study were to investigate the tropism of viruses present in the cellular reservoir in a group of patients under suppressive HAART and to determine the potential impact of the evolution of tropism.

Thirty-four naive patients, all HIV-1 subtype B infected, enrolled in the Hippocampe-ANRS 121 trial comparing regimens including protease inhibitors or non-nucleoside reverse transcriptase inhibitors, were studied [13]. These patients harboured HIV-1 plasma viral loads less than 50 copies/ml after 48 weeks of HAART except for three patients (Table 1). V3 *env* was amplified and sequenced from plasma and peripheral blood mononuclear cells (PBMC) at baseline and in PBMC at week 48. HIV-1 co-receptor usage was determined from the V3 *env* region sequence by Geno2pheno (http://coreceptor.bioinf.mpi-sb.mpg.de/cgi-bin/coreceptor.pl) and PSSM algorithms (http://ubik.microbiol.washington.edu/computing/pssm/) [14,15]. Viruses were classified into two categories: those with a lack (R5) or presence of X4-tropic viruses (R5X4 or X4). HIV-1 proviral DNA was quantified at baseline and week 48 as previously described [16].

At baseline, 22 out of 34 patients harboured a majority of R5 variants and X4 or R5X4 variants were predominant in 12 out of 34 patients in plasma and PBMC (Table 1). The same tropism was observed in plasma and PBMC for all patients. There was a switch from R5 to R5X4 variants at week 48 in only one of the 22 patients who harboured R5 variants at baseline. Patients harbouring R5X4/X4 variants at baseline had significantly lower CD4 T-cells counts (median 112 ± 106 and 269 ± 104 cells/μl, $P = 0.03$) and higher HIV-1 proviral DNA (median 3.4 ± 0.3 and $2.9 \pm 0.4 \log_{10}$ copies per 10^6 cells, $P = 0.004$) than patients with R5 variants. At week 48, only HIV-1 proviral DNA remained significantly different between patients harbouring R5 and R5X4/X4 viruses (median 2.56 ± 0.3 and $2.72 \pm 0.51 \log_{10}$ copies per 10^6 cells, respectively, $P = 0.004$). CD4 T-cell counts tended to be lower in patients harbouring R5X4/X4 variants than in patients harbouring R5 viruses (median 352 ± 163 and 457 ± 197 cells/μl, respectively, $P = 0.21$).

These results suggest that the tropism of viruses present in the reservoir cells did not change after 48 weeks of suppressive HAART despite the increase in CD4 cells as a result of the expansion of naive cells. The discrepancy

Table 1. HIV plasma and cell viral load, CD4 cell count and HIV-1 tropism evolution between baseline and week 48 under HAART.

	Day 0				Week 48			
Patient	RNA viral load (copies/ml)	DNA viral load ($log_{10}/10^6$ cells)	CD4 cell count (cells/μl)	Tropism plasma/PBMC	RNA viral load (copies/ml)	DNA viral load ($log_{10}/10^6$ cells)	CD4 cell count (cells/μl)	Tropism plasma/PBMC
1	25400	2.28	332	R5	50	1.69	790	R5
2	47000	3.04	338	R5	50	2.58	533	R5
3	240000	3.48	338	R5	50	2.79	574	R5
4	190184	2.46	211	R5	50	2.46	291	R5
5	212731	2.94	214	R5	50	2.72	473	R5
6	125000	3.33	285	R5	50	2.7	542	R5
7	33400	3.11	206	R5	50	2.5	532	R5
8	142000	2.5	31	R5	50	2.59	187	R5
9	511000	3.66	135	R5	50	2.47	157	R5
10	122000	2.6	275	R5	50	2.57	457	R5
11	5514	2.74	287	R5	50	2.57	374	R5
12	73082	3.11	276	R5	50	2.27	424	R5
13	412600	2.38	141	R5	50	2.38	381	R5
14	283900	3.6	405	R5	50	3.09	942	R5
15	1645000	2.44	17	R5	50	2.6	153	R5X4
16	145455	2.85	213	R5	50	2.18	341	R5
17	114533	2.96	263	R5	50	2.36	480	R5
18	71795	2.89	294	R5	50	2.39	631	R5
19	544000	3.37	304	R5	50	2.62	389	R5
20	89500	2.69	217	R5	50	2.56	631	R5
21	157430	2.62	32	R5	50	1.54	123	R5
22	137105	2.98	277	R5	50	2.72	406	R5
23	606000	3.47	108	R5X4	50	2.67	385	R5X4
24	312000	3.51	248	X4	50	2.64	502	X4
25	218437	3.26	251	R5X4	50	2.72	562	R5X4
26	3876110	3.47	12	X4	81	2.49	224	X4
27	85500	2.94	322	R5X4	50	2.8	406	R5X4
28	811140	3.82	80	R5X4	101	3.62	661	R5X4
29	161293	3.13	116	X4	50	2.61	241	X4
30	750000	3.18	18	R5X4	74	2.41	170	R5X4
31	81900	3.6	280	R5X4	50	3.6	553	R5X4
32	27100	2.77	59	R5X4	50	2.77	352	R5X4
33	294200	3.68	99	R5X4	50	2.93	236	R5X4
34	67560	3.29	199	R5X4	50	4.1	351	R5X4

PBMC, Peripheral blood mononuclear cell.

with a previous study could be explained by the type of regimen or different time of analysis [8].

In the present study, patients harbouring X4 strains had significantly lower CD4 T-cell counts than patients harbouring R5 strains. After 48 weeks of HAART, this difference did not remain significant, but patients with R5X4/X4 viruses tended to have lower CD4 T-cell counts, even though the CD4 T-cell counts had increased from baseline. These results are in accordance with those of the HOMER cohort, in which the CD4 cell counts in subjects harbouring X4 variants were, on average, three times lower than those in subjects harbouring exclusively R5 variants [17]. In addition, there is a link between the presence of R5X4/X4 strains and the level of HIV-1 proviral DNA: the presence of X4 viruses was associated with higher HIV-1 proviral DNA at baseline and after 48 weeks of HAART, in comparison with R5 variants, and this difference remained significant despite the decrease in HIV-1 proviral DNA induced by HAART. It has been shown that the presence of X4 viruses clearly increases the risk of disease progression and this could be related to a higher rate of HIV-1 proviral DNA [17]. R5 and X4 viruses do not infect all CD4 T cells with equal efficiency, probably because of the differences in co-receptor expression [18,19]. This co-receptor expression pattern may thus be critical to explain the differences in integration of HIV-1 DNA in host cells.

In conclusion, in the group of patients receiving HAART studied here, X4 variants did not emerge in the reservoir over time. This study suggests that the use of CCR5 antagonists should not be compromised in patients harbouring R5 viruses before starting fully suppressive HAART without R5 antagonists. As the emergence of X4 viruses in plasma during treatment with R5 antagonists has been described for a minority of treated patients, it will be interesting also to study the reservoir and its possible evolution in the context of R5 antagonist treatment.

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Treatment response to ritonavir-boosted tipranavir versus ritonavir-boosted lopinavir in HIV-1 patients with higher lopinavir mutation scores

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Week 48 HIV-RNA treatment response to the protease inhibitor tipranavir co-administered with ritonavir was compared with that of lopinavir co-administered with ritonavir in patients whose baseline isolates had varying lopinavir genotypic mutation scores. With increasing lopinavir mutation scores, the proportion of patients achieving a week 48 treatment response was increased in the tipranavir/ritonavir compared with the lopinavir/ritonavir arm. Tipranavir/ritonavir therapy improves treatment response rates compared with lopinavir/ritonavir in patients whose viruses have reduced susceptibility to lopinavir/ritonavir.

Tipranavir (Aptivus) is a non-peptidic, protease inhibitor with potent *in vitro* activity against the majority of protease inhibitor-resistant HIV-1 strains [1–4]. Low-dose ritonavir is co-administered with tipranavir to ensure that therapeutic levels of tipranavir are achieved [5,6]. Tipranavir/ritonavir has potent activity against HIV-1 in treatment-naive [7] and treatment-experienced patients [8]. In patients who have previously received two or more protease inhibitor-based regimens, tipranavir/ritonavir is effective and well tolerated [8–10].

The RESIST-1 and -2 studies are multicenter, open-label phase III trials evaluating the efficacy and safety of tipranavir/ritonavir (500 mg/200 mg twice a day) compared with an investigator-selected, ritonavir-boosted comparator protease inhibitor (CPI) chosen from amprenavir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir, and saquinavir/ritonavir. These were administered with an optimized background regimen (OBR), including two or more reverse transcriptase inhibitors, with or without the HIV-1 fusion inhibitor enfuvirtide, in triple-class antiretroviral therapy-experienced HIV-1-infected patients [8]. The trials were designed to have at least a triple combination antiretroviral regimen. The most

appropriate CPI/ritonavir and OBR were selected for each patient by the investigator guided by resistance testing, before the 1 : 1 random assignment of 1483 patients into the tipranavir/ritonavir and CPI/ritonavir groups. Antiviral resistance expert input was available to assist with the choice of OBR and the best possible CPI/ritonavir.

The study designs of RESIST-1 and -2 were similar allowing data from both trials to be combined for analysis. Tipranavir/ritonavir gave superior and more durable virological and immunological responses than CPI/ritonavir at weeks 24, 48 and 96 of the RESIST studies [8,11,12].

In a subanalysis of RESIST data, the week 48 HIV-RNA treatment responses to tipranavir/ritonavir and to lopinavir/ritonavir were compared in patients whose baseline isolates had different lopinavir genotypic mutation scores to identify the impact of this score on the virological activity of lopinavir/ritonavir compared with tipranavir/ritonavir. The lopinavir mutation score previously described and validated was derived by totaling the number of the following lopinavir-associated genotype mutations present: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, and L90M [13]. The lopinavir mutation score may be useful in interpreting HIV genotypic resistance testing with respect to lopinavir/ritonavir-based regimens [13].

Treatment response rates (confirmed viral load reduction $\geq 1 \log_{10}$ copies/ml at week 48 without viral rebound; confirmed viral load $< 1 \log_{10}$ copies/ml below baseline), and the proportion of patients with viral loads less than 400 and less than 50 copies/ml at week 48 were determined for patients not taking lopinavir/ritonavir at screening and randomly assigned to receive either tipranavir/ritonavir or lopinavir/ritonavir. Genotypic sensitivity scores (GSS) for background drugs in the regimen were compiled. GSS represents the sum of genotypically sensitive background drugs in the regimen, with higher scores indicating the presence of more active drugs.

Of the lopinavir/ritonavir stratum patients for whom lopinavir/ritonavir was not in use at screening, 164 were randomly assigned to tipranavir/ritonavir and 150 to lopinavir/ritonavir. Baseline characteristics were similar in both treatment arms of the lopinavir/ritonavir stratum. For the tipranavir/ritonavir arm, the median baseline characteristics were 181 CD4 cells/μl, viral load $4.53 \log_{10}$ copies/ml, and a lopinavir mutation score of five. For the lopinavir/ritonavir arm, the median baseline characteristics were 140 CD4 cells/μl, viral load $4.71 \log_{10}$ copies/ml, and a lopinavir mutation score of six.

At baseline, phenotypic data were available for 75 isolates. The median fold changes in IC_{50} to tipranavir were 0.7, 1.9, 1.9 and 2.7 if the lopinavir scores were up to three, four to five, six to seven and more than seven, respectively. The fold change in IC_{50} to lopinavir was 1.4, 17.8, 41.3 and 94.5 if the lopinavir scores were up to three, four to five, six to seven and more than seven, respectively. Lopinavir clinical phenotypic cut-offs were less than 10-fold, greater than 10 and less than 40-fold and 40-fold and greater. Tipranavir clinical phenotypic cut-offs were between zero and three-fold, between more than three and 10-fold and greater than 10-fold.

International AIDS Society treatment guidelines emphasize the goal of sustained viral suppression to less than 50 copies/ml with newer antiretroviral agents, even in treatment-experienced HIV-1 patients [14]. With this efficacy endpoint in mind, a viral load less than 50 copies/ml was evaluated. In patients with up to three lopinavir mutations, the proportion of patients achieving a viral load less than 50 copies/ml was comparable between the two treatment arms (Table 1). For patients with a

Table 1. Week 48 virological responses in lopinavir stratum[a] stratified by lopinavir mutation score.

			TPV/r ($N = 164$)		LPV/r ($N = 150$)	
			n/N	%	*n/N*	%
Treatment response	LPV mutation score	0–3	19/42	45.2	15/30	50.0
		4–5	30/54	55.6	16/41	39.0
		6–7	19/53	35.8	14/64	21.9
		>7	5/15	33.3	1/15	6.7
Viral load < 400 copies/ml	LPV mutation score	0–3	21/42	50.0	16/30	53.3
		4–5	29/54	53.7	16/41	39.0
		6–7	17/53	32.1	12/64	18.8
		>7	5/15	33.3	1/15	6.7
Viral load < 50 copies/ml	LPV mutation score	0–3	17/42	40.5	13/30	43.3
		4–5	24/54	44.4	11/41	26.8
		6–7	14/53	26.4	8/64	12.5
		>7	4/15	26.7	0/15	0.0

LPV, Lopinavir; TPV, tipranavir; /r, boosted with ritonavir. *n*, Number of responders, *N*, number of evaluable patients. The data did not reach significance because of low patient numbers.
[a]Refers to lopinavir/ritonavir stratum patients who were not taking lopinavir at the time of screening for the RESIST studies.

lopinavir mutation score greater than three, the proportion with a viral load less than 50 copies/ml was consistently higher in the tipranavir/ritonavir arm compared with the lopinavir/ritonavir arm. The most pronounced difference in viral suppression was observed at the highest lopinavir mutation score (more than seven), with 26.7% versus 0% of patients achieving a viral load less than 50 copies/ml in the tipranavir/ritonavir and lopinavir/ritonavir arms, respectively.

GSS for background reverse transcriptase inhibitors and enfuvirtide were compared for patients taking tipranavir/ritonavir or lopinavir/ritonavir, stratified by the lopinavir mutation score. The percentage of patients with enfuvirtide in the OBR was similar in each group (23.2% of tipranavir/ritonavir recipients and 22.0% of lopinavir/ritonavir recipients). The median GSS was two in all groups, except for patients in the tipranavir/ritonavir group with a lopinavir score greater than seven, when it was one. There were no significant differences between the groups for GSS, suggesting that the availability of active background drugs was similar for patients in both treatment groups. Therefore, it is unlikely that the more favorable responses observed in tipranavir/ritonavir recipients were the result of a more active OBR. If GSS scores are assessed according to response, non-responders in both the tipranavir/ritonavir and lopinavir/ritonavir groups had a similar number of patients with low GSS scores, whereas among responders in both the tipranavir/ritonavir and lopinavir/ritonavir groups the majority of patients had higher GSS scores.

Forty-eight week efficacy data from the RESIST trials has demonstrated that, for patients not taking lopinavir/ritonavir at screening, the proportion of patients who achieved a viral load less than 50 copies/ml in the tipranavir/ritonavir arm was greater than in the lopinavir/ritonavir arm [8]. Tipranavir/ritonavir represents an attractive treatment option in combination with an OBR for highly treatment-experienced patients [8]. Furthermore, in the patients whose baseline isolates were interpreted as having genotypic susceptibility to lopinavir despite having more than three lopinavir score mutations, virological responses were superior in the tipranavir/ritonavir arm compared with the lopinavir/ritonavir arm. Of the patients who were infected with virus with a reduced phenotypic susceptibility to lopinavir/ritonavir (all with more than three lopinavir score mutations), the proportions that achieved viral loads less than 50 copies/ml were consistently higher in the tipranavir/ritonavir arm compared with the lopinavir/ritonavir arm. Patients on treatment who experience persistent low-level viremia are at an increased risk of virological failure, emphasizing the need to optimize treatment and maintain an undetectable viral load of less than 50 copies/ml [15–17]. Tipranavir/ritonavir demonstrates the ability to achieve a sustained viral suppression to less than 50 copies/ml in many patients with reduced susceptibility to lopinavir.

Recent guidelines recommend that the main goal of therapy should be the suppression of viremia below detection limits even in treatment-experienced patients [8,14]. The results of this study suggest that tipranavir/ritonavir has the potential to achieve these recommended outcomes, particularly in patients whose HIV-1 isolates demonstrate reduced susceptibility to lopinavir/ritonavir.

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Conflicts of interest: S.L.W. is a consultant on advisory boards, speaker bureaus, and has participated in the conduct of clinical trials with Boehringer Ingelheim, Roche, Abbott, Bristol-Myers Squibb (BMS), GlaxoSmithKline (GSK), Gilead, Tibotec, Merck, Pfizer, and Agouron. L.C. is a consultant on advisory boards for BMS, Boehringer Ingelheim, GSK and Roche and has participated in clinical trials for Abbott, Boehringer Ingelheim, BMS, Gilead, GSK, Merck, Pfizer, Roche and Tibotec. S.R. has received research support or honoraria from Abbott, Boehringer Ingelheim, BMS, Gilead and GSK. He has also served as a consultant to Abbott, Gilead, GSK and Janssen-Cilag. D.J.W. is a consultant to, serves as a speaker, and has research grants from BMS, Boehinger Ingelheim, Gilead, GSK, Roche and Tibotec, and has research grants from Merck, Pharmasset and Tanox. C.B.H. is not an employee or a shareholder of stock in any company and has grant support from Abbott, Boehringer Ingelheim, BMS, Gilead, GSK, Tibotec, Merck, and Pfizer. He has served as a speaker for, an advisor to and received honoraria from Abbott, Boehringer Ingelheim, BMS, Gilead, GSK, Tibotec, Pfizer, and Roche. U.M. and H.V. were both employees of Boehringer Ingelheim. C.A.B.B. is consultant for Abbott, Roche, BMS, Glaxo Wellcome, and Boehringer Ingelheim.

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Increased incidence of cutaneous mycoses after HAART initiation: a benign form of immune reconstitution disease?

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Immune reconstitution disease (IRD) has been associated with many pathogens after the initiation of antiretroviral therapy for advanced HIV infection. A retrospective cohort study was conducted to determine whether cutaneous mycoses were also associated with IRD. After adjusting for various confounding factors, the recent initiation of HAART was found to be associated with an increased incidence of cutaneous mycoses when compared with untreated patients.

Immune reconstitution after HAART initiation is frequently complicated by adverse clinical manifestations corresponding to either the unmasking of pre-existing untreated opportunistic infections or the clinical deterioration of a known and treated opportunistic infection [1]. The pathogens involved in this IRD (bacteria, parasites, viruses, or fungi) stimulate a dysregulated inflammatory response, notably during the initial rapid recovery of immune functions in severely immunodeficient patients having initiated HAART. Superficial and systemic mycoses are a major cause of morbidity and mortality among patients living with HIV. IRD has been described with fungal agents such as *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Pneumocystis jiroveci*. There is, however, little literature on cutaneous mycoses. Our objective in the present study was to determine factors associated with cutaneous mycoses in French Guiana and whether the initiation of HAART was followed by an increase in the incidence of cutaneous mycoses.

HIV-positive patients followed in Cayenne, Kourou, and Saint Laurent du Maroni Hospitals between 1 January 1996 and 31 December 2006 were enrolled in the French Hospital Database for HIV (FHDH) and right censoring occurred after the last visit. Time-independent variables such as sex, nationality, mode of transmission, and time-dependent variables such as age, CD4 cell counts, HIV-1 viral loads, treatments, and clinical events (that is cutaneous mycoses) are time-referenced and routinely entered by trained clinical studies technicians. Diagnoses are coded according to the 10th International Classification of Diseases. Therefore, specific details such as the size and exact topography of the lesion could not be obtained from the database. Patients included in the FHDH give informed consent to the use of their data. Their identity is encrypted before the data are sent to the Ministry of Health and the Institut National de la Recherche Médicale (INSERM), which centralize data from Centers for Information and Care of HIV (CISIH)

throughout France. This data collection is approved by the Commission Nationale Informatique et Libertés (CNIL). The data were analysed using STATA version 8.0 (STATA Corp., College Station, Texas, USA).

In this retrospective cohort study, a multiple failure Cox proportional hazards model was used to evaluate the adjusted relationship between failure and explanatory variables. The failure event was the incidence of cutaneous mycosis. Because a patient may develop a cutaneous mycosis more than once we used a multiple failure model in which data from the patients are still considered after they presented a first failure event [2]. The main explanatory variables were age, sex, transmission mode, nationality (French citizens versus non-French citizens), CD4 cell count at the time of the visit (categorized as <200, 200–499, and >500 cells/μl), the presence or absence of HAART, time since first treatment started (<2 months, 2–4 months, 4–6 months, 6–12 months, >12 months). The proportionality of the hazard functions was determined using Schoenfeld and scaled Schoenfeld residuals and the global proportional hazards test. Age, nationality, CD4 cell count category at the time of HIV diagnosis, and follow-up duration were transformed into dummy variables to compare different groups with a reference group. Because the period that follows HAART initiation is scrutinized more carefully than routine follow-up, time to a clinical event may have been biased by this change in the frequency of consultations. An adjustment variable was created that tried to control for this difference. The ratio between the number of consultations per time unit during each period was generated and added to the Cox model. In addition, because nevirapine, efavirenz and abacavir are known to have frequent cutaneous adverse effects, adjustments were made for these molecules using a single composite variable in order to control for a possible cutaneous orientation of the clinicians' attention.

A total of 1647 subjects with 27 662 observations were included, representing a total of 5902 person-years of follow-up. The median follow-up was 2.99 years. There were 109 clinical episodes of cutaneous mycoses recorded in 106 patients. Among these, 75 were reported as 'dermatophytosis', 26 were reported as 'cutaneous mycosis' without specification, and eight were reported as 'candidosis of the skin or nails'.

Table 1 shows that after adjusting for potential confounders there was an increased incidence of cutaneous mycoses in the months after HAART initiation. This tended to decrease with time until 6 months after the initiation of antiretroviral treatment. Table 1 also shows that men and foreign citizens were more likely to develop cutaneous mycoses. Although adjustments were made to control for the increased

Table 1. Crude incidence rates and adjusted hazard ratios for the advent of cutaneous mycoses.

	Time at risk (years)	Crude incidence rate (/100 person-years)	Adjusted hazard ratio[a] (95% CI)	*P*
Sex				
Male	2652	2.6	2.2 (1.4–3.5)	0.001
Female	3251	1.3		
Age (years)				
0–29	1045	1.7	1.1 (0.4–3)	0.8
30–39	1844	1.8	0.9 (0.4–2.1)	0.7
40–49	1740	2.3	0.9 (0.4–2.2)	0.9
50–59	833	1.6	0.5 (0.2–1.4)	0.2
>60	441	2	1	
Transmission mode				
Heterosexual	5089	2	1.4 (0.6–2.9)	0.4
Other	814	1.7		
Nationality				
French	1163	1.3	1	
Non-French	3535	2.3	2.17 (1.2–4)	0.01
CD4 cell count				
<200	1554	2.5	1	
200–499	2757	1.7	0.7 (0.5–1.2)	0.2
>499	1242	1.3	0.6 (0.3–1.2)	0.15
Period relative to HAART				
Before HAART	2322	1.1	1	
≤2 months	82	7.3	10.2 (3.7–28.5)	<0.001
>2–4 months	124	4	3.8 (1.2–12.5)	0.03
>4–6 months	112	4.5	3.8 (1.2–11.9)	0.03
>6–12 months	135	2.2	0.9 (0.1–6.7)	0.9
>12 months	3127	2.2	1.7 (0.9–3)	0.1

CI, Confidence interval.
[a]Obtained using a multiple failure Cox proportional hazards model including CD4 cell counts, sex, nationality, age, presence or absence of HAART, duration of HAART, transmission mode, a composite variable indicating the presence of nevirapine, efavirenz or abacavir, and an adjustment variable consisting of the number of visits per period of time.

frequency of consultations after HAART initiation and for the presence of molecules notoriously responsible of cutaneous adverse effects, this may not have been sufficient to control for all the differences that may have occurred. Adherence issues and the search for toxicities are, however, usually more specifically targeted than the search for mycoses. Therefore, there may indeed be a real increase in the incidence of cutaneous mycoses. This could represent a benign form of IRD in which the pathogen is unmasked by the restored immune system. Clinicians should thus be attentive to superficial mycoses after HAART initiation.

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