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Increasing prevalence of transmitted drug resistance mutations and non-B subtype circulation in antiretroviral-naive chronically HIV-infected patients from 2001 to 2006/2007 in France

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Objectives: To estimate the prevalence of transmitted drug resistance mutations and non-B subtype circulation in antiretroviral-naive chronically HIV-1-infected patients in France.

Methods: Resistance mutations were sought in samples from 530 newly diagnosed HIV-1-infected patients from October 2006 to March 2007. Protease and reverse transcriptase mutations were identified from the 2007 Stanford Resistance Surveillance list.

Results: Reverse transcriptase and protease resistance mutations were determined in 466 patients with duration of seropositivity <5 years. 42% of patients were infected with non-B subtype strains (CRF02 18.3%). The overall prevalence of viruses with protease or reverse transcriptase mutations was 10.6% (95% confidence interval 6.7–16.3). The prevalence of protease inhibitor, nucleoside reverse transcriptase inhibitor and non-nucleoside reverse transcriptase inhibitor resistance-associated mutations was 4.7%, 5.8% and 2.8%, respectively. Frequency of resistance was not different in patients infected with B (9.5%) and non-B (CRF02 7.8% and other 11.2%) subtypes. Baseline characteristics such as gender, age, transmission group, country of transmission, disease stage, CD4 counts and viral load were not associated with the prevalence of transmitted drug resistance.

Conclusions: In France in 2006/2007, the prevalence of transmitted drug-resistant variants was 10.6%. Prevalence of transmitted drug resistance was comparable in B and non-B subtypes. Prevalence of non-B subtypes is still rising.

Keywords: HIV-1, resistance surveillance, France

Introduction

HIV-1 drug resistance is one of the major factors associated with virological failure to antiretroviral therapy.[1] It is considered that the origin of resistant HIV-1 is mainly the selection of resistant variants in patients with virological failure on antiretroviral therapy.

However, the transmission of drug-resistant viruses can contribute to the expansion of resistance. Although both acquired and transmitted HIV-1 drug resistance are public health concerns, transmitted resistance has the potential to reverse more rapidly the effectiveness of first-line antiretroviral therapy at the population level. Persons with transmitted drug resistance begin antiretroviral therapy with a lower genetic barrier to resistance, a higher risk of virological failure and a higher risk of developing resistance even to those drugs in their regimen that were originally fully active.[2–5] Surveillance of transmitted resistance can supply information to support recommendations for resistance testing in this clinical setting.

The objective of this study was to survey the frequency of resistance mutations and the spread of non-B HIV-1 subtypes in a representative sample of antiretroviral-naive patients with chronic infection in 2006/2007 (Odyssee study) in France. The results of the Odyssee 2006/2007 study were compared with those of the previous survey, Odyssee 2001.[6]

Patients and methods

Study population

The study population comprised 530 treatment-naive chronically infected patients (up to 20 consecutive HIV-1-diagnosed patients in each virology laboratory with complete HIV-1 western blot profiles) managed in 31 specialized AIDS centres throughout France. Patients were enrolled from October 2006 to March 2007. The study was approved by the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS) and the Commission nationale de l'informatique et des libertés (CNIL). All patients gave written informed consent to participation in the study.

Enzyme immunoassay to detect recent HIV-1 infection

As previously described, the enzyme immunoassay to detect recent HIV-1 infection (EIA-RI) assay was developed to detect recent HIV infection, within 180 days from infection to diagnosis, on dried serum spot samples.[7] The algorithm used in our study was that described by Barin *et al.*[7]

Genotypic resistance analyses

Genotypic resistance studies were performed on plasma viral RNA by using the consensus technique of the ANRS Resistance Study Group, the TruGene HIV-1 genotyping kit (Siemens Healthcare, Eragny, France), or the ViroSeq sequencing-based HIV-1 genotyping kit (Abbott, Rungis, France). Protease and reverse transcriptase (RT) mutations were identified from the consensus statement of the list for genotypic surveillance of transmitted HIV-1 drug resistance [protease inhibitors (PIs): L24I, D30N, V32I, M46I, I47A/V, G48V, I50V/L, F53L, I54V/L/M/A/T/S, G73C/S/T/A, V82A/F/T/S/M, I84V/A/C, N88D/S, L90M; nucleoside reverse transcriptase inhibitors (NRTIs): M41L, K65R, D67N/G/Del, T69D/Ins, K70R, L74V, V75A/M/T/S, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, F215Y/F/C/D/E/S/I/V, K219Q/E/R; non-nucleoside reverse transcriptase inhibitors (NNRTIs): L100I, K101E, K103N/S, V106A/M, Y181C/I, Y188L/H/C, G190A/S/E/Q, P225H, M230L, P236L].[8] Amino acid sequences stored from the previous survey (Odyssee 2001) were also re-analysed using the list for genotypic surveillance of transmitted HIV-1 drug resistance to allow comparisons of the frequencies of transmitted drug resistance between the two surveys.[6] All the virology laboratories involved in these studies have participated in the French national quality control studies.[9]

Phylogenetic analyses

HIV-1 subtype was determined by phylogenetic analysis of RT sequences. The nucleotide sequences were aligned by Clustal W1.74 with known reference strains of groups M, N and O. Phylogenetic trees were inferred using the neighbour-joining method and two Kimura parameters with 1000 bootstrap values. Clusters of sequences were confirmed by constructing phylogenetic trees from RT sequences using the maximum likelihood method with a PhyML algorithm and using a discrete gamma model of nucleotide substitution (HKY85). Robust clusters were identified by high bootstrap values (98%) with 1000 re-samplings and short branch lengths (total of genetic distances within cluster 0.02).[10,11]

Statistical analyses

The χ^2 test or the Fisher exact test was used, as appropriate, to compare categorical variables, and the Mann–Whitney *U*-test was used to compare continuous variables. The 95% confidence intervals (CIs) were computed using a binomial distribution. Links between transmitted drug resistance mutations and sex, age, risk factors, clinical stage, duration of known seropositivity, CD4 cell counts and plasma viral load were tested, together with links between the HIV-1 subtype and the other factors. Weighted analyses were used to derive representative estimates of the percentage of patients with resistance mutations.[12] The weight of each centre was attributed on the basis of the number of patients treated in each centre, as stated in the French Hospital Database on HIV infection.[13] Statistical analyses were performed using Stata 10 software (Houston, TX, USA).

Results

Characteristics of the population

The baseline characteristics of the patients included in the Odyssee 2001 and 2006/2007 surveys are shown in Table 1. About half of the patients included in the two surveys lived in the Paris area. The other patients were distributed all over France, including the French West Indies. The EIA-RI was performed in 276 patients from the Odyssee 2006/2007 study only. Ten out of the 276 (3.6%) patients were found to have been infected for less than 6 months. In the Odyssee 2001 study, the median duration of known seropositivity was 0.56 years [interquartile range (IQR) 0–18.1]. All patients enrolled in the Odyssee 2006/2007 survey had a duration of known seropositivity of less than 5 years with a median of 0.2 years (IQR 0–1.6).

Transmitted genotypic drug resistance

Among the 404 and 530 patients from the Odyssee 2001[6] and 2006/2007 studies, protease and RT transmitted drug resistance mutations were determined in 363 and 466 patients, respectively. As reported in Table 2, the overall weighted prevalence of viruses with at least one protease or RT drug resistance mutation

Table 1. Patient baseline characteristics in Odyssee 2001 and Odyssee 2006/2007 surveys

	Odyssee 2001				Odyssee 2006/2007			
Study characteristics	all patients weighted, $n=363$	B subtype weighted, $n=240$	non-B subtype weighted, $n=119$	*P* value	all patients weighted, $n=466$	B subtype weighted, $n=273$	non-B subtype weighted, $n=193$	*P* value
Men, *n* (%)	248 (68.3)	187 (78.0)	56 (47.5)	<0.001	339 (72.7)	248 (73.1)	91 (47.1)	<0.001
Transmission group				<0.001				<0.001
homosexual men, *n* (%)	113 (31.2)	91 (37.9)	19 (16.0)		223 (47.9)	202 (74.0)	21 (10.9)	
heterosexual men and women, *n* (%)	186 (51.2)	99 (41.3)	86 (72.3)		202 (43.3)	55 (20.1)	147 (76.2)	
other, unknown, *n* (%)	64 (17.6)	50 (20.8)	14 (11.7)		41 (8.8)	16 (5.9)	25 (12.9)	
CDC stage, *n* (%)				0.170				0.887
A	261 (71.9)	181 (75.4)	76 (63.9)		378 (81.1)	222 (81.3)	156 (80.8)	
B	42 (11.5)	27 (11.3)	15 (12.6)		33 (7.1)	21 (7.7)	12 (6.2)	
C	60 (16.6)	32 (13.3)	28 (23.5)		55 (11.8)	30 (11.0)	25 (13.0)	
Patients from sub-Saharan Africa, *n* (%)	74 (20.4)	9 (3.7)	65 (54.6)	<0.001	112 (24.0)	7 (2.6)	105 (54.4)	<0.001
Median CD4 cells/mm^3, (range)	385 (2–1280)	406 (2–1280)	279 (2–1237)	0.008	352 (2–1758)	384 (6–1758)	323 (2–1090)	0.051
Median HIV-1 plasma RNA, log copies/mL (range)	4.5 (<2.3–6.9)	4.5 (<2.3–6.9)	4.4 (<2.3–6.4)	0.993	4.5 (<2.3–6.6)	4.5 (<2.5–6.6)	4.4 (<2.3–6.4)	0.460
Median duration of known seropositivity, years (range)	0.56 (0–18.1)				0.2 (0–1.6)			
<6 months, *n* (%)	180 (49.5)	100 (41.9)	76 (64.2)	0.003	275 (59.0)	163 (59.7)	112 (58.0)	
6 months to 2 years, *n* (%)					86 (18.5)	59 (21.6)	27 (14.0)	
2 years to 5 years, *n* (%)					105 (22.5)	51 (18.7)	54 (28.0)	0.070

increased significantly from 2001 to 2006/2007 (3.9% versus 10.6%, respectively; $P<0.001$). The results were similar for subtypes A and B.

Table 2. Weighted prevalence (%) of virus with at least one PI, NRTI or NNRTI drug resistance mutation in Odyssee 2001 and 2006/2007 studies

	Odyssee 2001	Odyssee 2006/2007	*P* value
All patients (*n*)	363	466	
at least one ARV, % (95% CI)	3.9 (2.6–6.0)	10.6 (6.7–16.3)	<0.001
PIs, % (95% CI)	0.8 (0.3–1.7)	4.7 (1.9–11.3)	0.001
NRTIs, % (95% CI)	3.4 (2.1–5.4)	5.8 (2.9–11.1)	0.101
NNRTIs, % (95% CI)	0.3 (0.1–1.4)	2.8 (6.7–16.3)	0.005
Subtype B HIV-1-infected patients (*n*)	240	273	
at least one ARV, % (95% CI)	4.2 (2.0–7.5)	11.0 (7.5–15.3)	0.005
PIs, % (95% CI)	0.4 (0.0–2.3)	4.0 (2.0–7.1)	0.006
NRTIs, % (95% CI)	3.8 (1.7–7.0)	6.2 (3.7–9.8)	0.144
NNRTIs, % (95% CI)	0.4 (0.0–2.3)	2.6 (1.0–5.2)	0.051

ARV, antiretroviral drug.

An increase in the weighted prevalence of virus with transmitted mutations associated with resistance to antiretroviral classes was observed between 2001 and 2006/2007. The frequency of viruses resistant to one class was 3.2% (95% CI 2.1–5.5) in 2001 versus 7.9% (95% CI 5.3–11.8) in 2006/2007. These results were 0.6% (95% CI 0.2–1.5) in 2001 versus 2.6% (95% CI 0.6–9.6) in 2006/2007 and 3.2% (95% CI 2.1–5.5) in 2001 versus 7.9% (95% CI 5.3–11.8) in 2006/2007 for two classes of antiretroviral drugs. Resistance to three classes of antiretroviral drugs was not found in 2001, whereas the frequency observed in 2006/2007 was 0.1% (95% CI 0.01–0.71). These differences were only significant for two classes of antiretroviral drugs ($P=0.001$).

Patients from the 2006/2007 survey harbouring PI, NRTI and NNRTI transmitted drug resistance mutations (unweighted results) are described in Tables 3, 4 and 5, respectively. The classic amino acid substitution at codon 215 (T215Y/F) was detected in one and three patients in 2001 and 2006/2007, respectively. On the other hand, atypical mutation profiles at this position (T215A/C/D/E/N/S/R/V) were detected in 9 (2.5%) and 24 (5.1%) patients in 2001 and 2006/2007, respectively.

The duration of known seropositivity had no significant impact on the global transmitted drug resistance prevalence rates in either survey. In Odyssee 2006/2007, no difference in baseline characteristics such as gender, age, transmission group, country of transmission, disease stage, median CD4 cell counts and median plasma viral load were observed between patients with and without transmitted mutant viruses.

Table 3. Changes in codons associated with resistance to PIs in Odyssee 2001 and 2006/2007 studies

		PI resistance-associated mutations													
Patients	HIV-1 subtype	L24	D30	V32	M46	I47	G48	I50	F53	I54	G73	V82	I84	N88	L90
Odyssee 2001															
418	CRF01				I										
720	B										S				M
1209			N												
1308	B				I						S				M
2202	B				I										
Odyssee 2006/2007															
3414	CRF01				I					V		A			
8909	B				I				L			AV			
8911	B			I	I					IV		A			LM
15811	B									V		A			
7501	CRF11/CRF13			I											
7515	B/CRF01										T		V		M
7516	B/CRF01										T		V		M
3204	B														M
8110	B				IM										
8114	A				IM										
6203	B														M
2404	B				I										M
4101	B									V					M
8504	A								FIST						M

Table 4. Changes in codons associated with resistance to NRTIs in Odyssee 2001 and 2006/2007 studies

		NRTI resistance-associated mutations														
Patients	HIV-1 subtype	M41	K65	D67	T69	K70	L74	V75	F77	Y115	F116	Q151	M184	L210	T215	K219
Odyssee 2001																
117	CRF02	R		G	P	R				F				F		
506	B	L													D	
511	B														E	
706	B			N										F		E
720	B			N		R										Q
726	B					R										
1205	CRF02			N												Q
1208	B															Q
1209	unknown										V					
1210	B															E
1219	B					R										
1302	B													W		
1308	B													W	H	
1312	B				D										C	
1414	B														E	
1710	B														N	
1713	D				S											
1912	B								L							
2205	B			N	D									W		
2207	CRF02												V		Y	
2210	B			N	D									W		
Odyssee 2006/2007																
12203	B													F	D	
3414	CRF01												I		F	
7328	B	L												W	S	
8612	B	L												W	SC	
8618	B	L													D	
5612	B	L												W	C	
5617	A			N	NS										V	Q
5904	CRF02								L							
5914	B													F	D	
5920	CRF02														A	
8815	B	L													C	
8904	B			N	D										D	Q
8911	B	L		N	N		I								C	E
7117	B														N	
7506	B														D	
7521	B	L													C	
3204	B	L												W	S	
3208	B	L													S	
7801	B	L													E	
8110	B	L													N	
2404	B			N	N								V		C	Q
2407	B			N	D									W	R	
2411	B														E	
4102	B	L													Y	
4104	B	L													C	
8504	A														CY	
8416	B	L												W	D	

Table 5. Changes in codons associated with resistance to NNRTIs in Odyssee 2001 and 2006/2007 studies

		NNRTI resistance-associated mutations									
Patients	HIV-1 subtype	L100	K101	K103	V106	Y181	Y188	G190	P225	M230	P236
Odyssee 2001											
415	B			N							
2207	CRF02			N							
Odyssee 2006/2007											
6705	B			N							
5818	A			N							
8812	B			N							
8816	B			N							
8904	B			N		C					
8909	B			NS							
8911	B							A			
15811	B			N							
3206	CRF02			N					H		
7809	B			N							
8113	CRF02					C					
6204	CRF02			N					H		

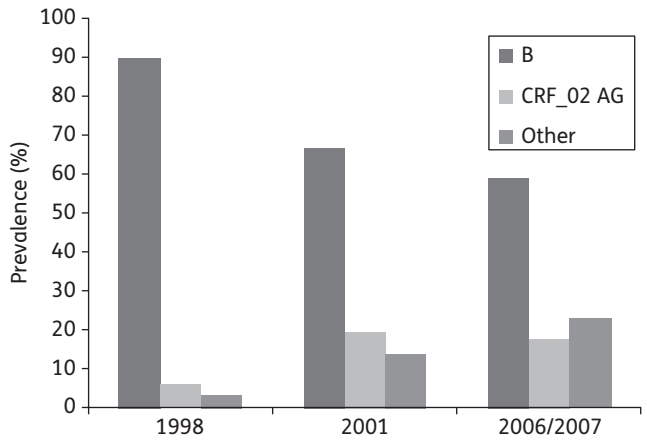

Figure 1. Prevalence of B and non-B subtypes in the Odyssee studies between 1998 and 2006/2007.

Phylogenetic analyses

In 2006/2007, the frequency of patients infected with a non-B subtype was 42%, with 84 (18%) patients being infected with CRF_02AG viruses (Figure 1). The proportions of patients with duration of known seropositivity <6 months, 6 months to 2 years and 2–5 years were not different according to B or non-B subtype. The frequency of transmitted drug resistance was not different according to subtype (B 11.1%, CRF_02AG 7.8%, other non-B subtypes 11.4%; $P=0.88$). A phylogenetic tree of sequences from 466 viruses revealed 26 clusters, including 55 patients with a number of individuals per cluster of 2 ($n=23$) and 3 ($n=3$). Twenty-two clusters included individuals living in the same geographical area. Among them, 10 clusters were composed of sexual partners. Seventeen clusters included subtype B viruses and nine included non-B viruses (A1 $n=3$, CRF_02AG $n=3$, D $n=1$, F2 $n=1$ and CRF_42 $n=1$). The overall prevalence of viruses with protease or RT transmitted drug resistance mutations was not different (11.8%) in this subset of patients from the total population of the study.

Discussion

The Odyssee studies are part of the French national multicentre surveillance of transmitted drug resistance in HIV-1-infected patients. These surveys were set up by the Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS) in 1998 and have been performed periodically since this date, in 2001 and 2006/2007.

The definition of transmitted drug resistance is still a matter of debate because of the potential impact of natural polymorphisms. In our study we therefore used the list of mutations for surveillance of transmitted drug resistance established by Shafer *et al.*[8] to define transmitted drug resistance. The previous 2001 French survey of transmitted drug resistance in naive chronically infected patients was analysed using the IAS-USA drug mutations resistance list available at that time.[6] In order to compare the results of the 2001 and 2006/2007 surveys, the 2001 resistance data were reanalyzed using the Shafer list.[8] Using this definition, the overall proportion of transmitted viruses resistant to at least one antiretroviral drug was estimated as around 4% in 2001, which increased significantly to nearly 11% in the 2006/2007 survey and reached the drug resistance prevalence of patients with acute primary infection. Indeed, in 2001 we found that patients with recent infection were more likely to harbour resistant HIV variants than were treatment-naive patients with chronic infection.[6,14] This might be explained by a lower risk of initial infection by a resistant virus in previous

years. In the Odyssee 2006/2007 survey, the rise in frequency of transmitted drug resistance was mainly due to a significant increase in the detection of mutations associated with resistance to PIs and NNRTIs, reflecting the broader use of these drugs in combination therapy. The frequency of transmitted drug resistance mutations observed in the 2006/2007 survey was roughly similar to the prevalence reported nowadays in other European countries as well as in North America in antiretroviral-naive chronically infected patients and in patients with acute primary infection, reflecting the same practices of patient care and the same types of drugs used in these areas.[2,3,14–22]

As in previous Odyssee surveys, we still found in 2006/2007 a higher proportion of atypical than classical substitutions at codon 215 of the RT gene. It is well known that these revertants, which are a signature of the broad usage of thymidine analogues in the past, are selected because they are fitter than their resistant counterparts.[23–25] These features might change in the future with the cessation of use of thymidine analogues in first-line therapy in developed countries.

In the Odyssee 2006/2007 survey, baseline characteristics such as gender, age, transmission group, country of transmission, disease stage, CD4 cell counts and plasma viral load were not associated with the prevalence of transmitted drug resistance, as already observed in the Odyssee 2001 study.[6] This was also observed in other surveys of transmitted drug resistance in acute primary infection.[14,16,20,21]

The frequency of patients infected with a non-B subtype reached 42% in 2006/2007, having increased significantly since 1998 (10%) and 2001 (33%).[6,26] This evolution in subtype distribution was mainly due to a higher proportion of patients originating from sub-Saharan countries. These patients were mostly women and patients whose disease was diagnosed at a late stage of infection, as noted in the French hospital database on HIV.[27] Although the proportion of CRF_02 (AG) viruses was stable around 20% between 2001 and 2006/2007, the increase in HIV-1 non-B subtypes was mainly due to a rising circulation of various CRF subtypes, accounting for higher diversity. The frequency of transmitted resistant variants was not different according to subtype, as already found in the previous Odyssee 2001 study. These results confirm the spread of non-B subtypes in France shown in resistance surveillance studies at the time of HIV-1 primary infection.[14]

The EIA-RI assay to detect HIV-1 infection of less than 6 months is routinely performed on HIV-1 diagnoses reported to the national HIV case surveillance in France.[28] In our study, this assay, performed in 60% of the subjects, showed that only 4.3% of them had a time since infection of less than 6 months. These results confirm that the population enrolled in our study was chronically infected and not recently infected, respecting the selection criteria. In the Odyssee 2001 study, patients with a duration of known seropositivity of less than 6 months were more frequently infected with non-B subtypes.[6] This was not observed in the 2006/2007 survey, in which the duration of known seropositivity was not different across HIV-1 subtypes.

In our study, the proportion of clusters was large compared with the size of the population reflecting the fact that HIV transmission in naive chronically infected patients is high at this clinical stage of HIV infection.[22,29–33] All clusters except three consisted of two individuals living in the same geographical area, suggesting that the subjects were closely related. This is not the case in primary or recent HIV infections, where clusters consist of multiple individuals.[29,30,32,33] It might be useful to compare these data with those observed in recent infections, looking for clusters between naive chronically infected subjects and subjects with acute primary infection.

In conclusion, in France in 2007, the difference observed in transmitted drug resistance frequencies between primary infection and naive chronically infected patients diminished over time, reaching the prevalence observed in Europe and North America. However, it is difficult to provide a clear prediction of the evolution of transmitted drug resistance. Thus, in developed countries the prevalence of HIV-infected patients receiving antiretroviral therapy with an undetectable viral load is increasing, lowering the risk of resistance transmission. By contrast, the situation in developing countries is more worrying. The use of antiretroviral therapy is hopefully becoming increasingly widespread, though most of the time without virological monitoring, and the frequency of drug resistance is increasing rapidly. This supports the need to continue the surveillance of transmitted drug resistance for all classes of antiretroviral drugs all around the world.

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